LYMPHOMA COALITION

SUBTYPE REPORT

Chronic Lymphocytic Leukaemia

March 2022

LYMPHOMA COALITION

Vision

Equity in lymphoma outcomes across borders.

Mission

Enabling global impact by fostering a lymphoma ecosystem that ensures local change and evidence-based action.

Acknowledgments

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Contents

Overview

Chronic lymphocytic leukaemia (CLL) is a mostly incurable cancer arising from the lymphocytes (white blood cells).[1] The clinical course of CLL is extremely variable, ranging from a slow-growing (indolent) disease not requiring treatment, sometimes never, to one that progresses rapidly (aggressive) and is resistant to treatment.[1] CLL typically affects older adults. Most cases of CLL are diagnosed in patients over the age of 55 years, with only approximately 10% of CLL cases being diagnosed in patients younger than 55 years.[2]

Over the last decade, there has been significant progress in CLL therapy and many new treatment options are available. Mainly, the development of novel (new) targeted therapies has improved treatment outcomes for many patients.[3] Additionally, there are now more accurate tests that can reliably define high-risk disease and guide treatment choice.[3]

The changing therapy landscape in CLL has made managing CLL more effective yet more challenging.[3]

There is no gold standard first- or second-line therapy regimens or further lines of therapy for CLL, and optimal therapy sequencing has not been established. With so many treatment options now available, doctors and patients are having to make very complex treatment decisions.

The focus of this report is to:

- Provide a current understanding of CLL
- Explain the diagnosis and pre-treatment process
- Outline CLL treatment options and protocols, including:
  - Therapy access in Lymphoma Coalition (LC) member countries
  - Clinical trial access in LC member countries
- Highlight Covid-19-related considerations for patients with CLL
- Explore the experience of patients with CLL

Major gaps that must be addressed in the treatment and care of patients with CLL include:

- First-line treatment requires optimisation to reduce the number of patients who develop disease relapse and need subsequent therapy.
- Therapy sequencing strategies must be optimized for existing and new treatments, in second line and beyond.
- Access to testing for genetic mutations, markers, and chromosomal abnormalities should be improved to ensure that all patients receive the best possible treatment.
- Access to targeted therapies must be improved globally as certain forms of CLL (e.g., del(17p) and/or *TP53* mutation, unmutated IGHV) respond poorly to chemoimmunotherapy.
- There is a continued need for better treatment options with fewer toxicities in all lines of therapy.
- Improved treatment options are needed for the diffuse large B-cell (DLBCL) variant of Richter's Transformation.
- There is a promising role for minimal residual disease (MRD) testing in treatment response assessment for CLL, but this needs to be defined for routine use in the clinic.
- A consensus guideline for the management of patients with CLL during the Covid-19 pandemic (and future pandemics) must be established, and clarity surrounding Covid-19 immunisation and care strategies for this patient population are needed.
- Patients with CLL require more support to manage both physical/medical issues (especially fatigue) and psychosocial issues. Patients in active surveillance require more support for specific psychosocial issues (e.g., fear of disease progression, anxiety, depression).
- There continues to be room for improvement in patient-doctor communication.

Words highlighted in **dark bold** are defined in the glossary at the end of the report.

Despite extensive research, it is not certain what exact mechanism triggers the process that causes CLL.

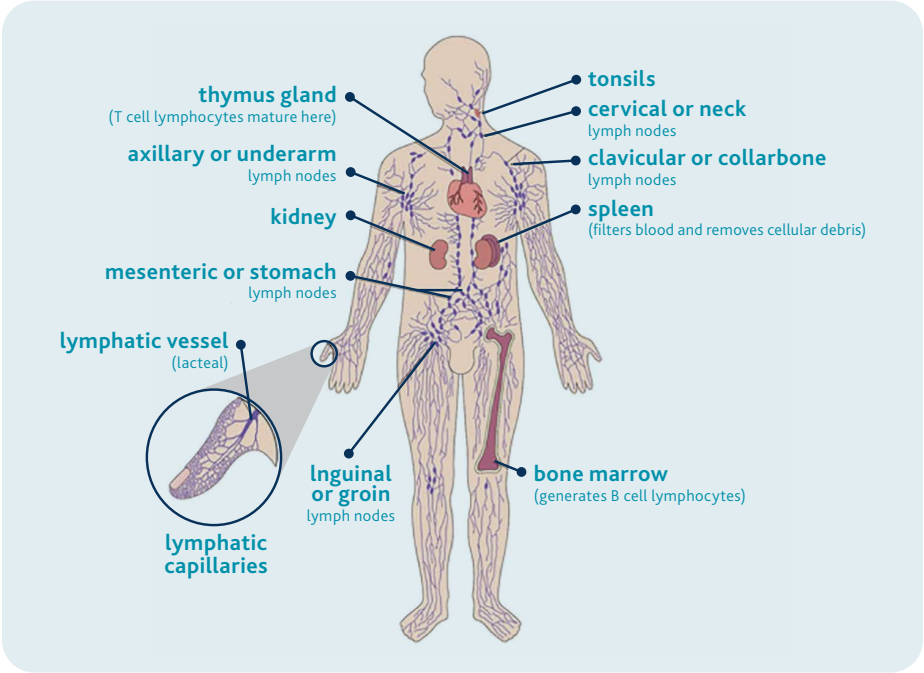
Understanding Chronic Lymphocytic Leukaemia (CLL)

LYMPHOMA

Lymphoma is a cancer of lymphocytes, a type of white blood cell.

Lymphocytes circulate in the body through a network referred to as the lymphatic system (figure 1). The organs and vessels of the lymphatic system work together to help fight infections throughout the body.

Figure 1. Lymphatic system, diagram adapted from The Open University, SXR376 Preparatory Reading



B lymphocytes (B cells) are responsible for creating antibodies or immunoglobulins which fight infections. T lymphocytes (T cells) either directly destroy cancerous cells and virally or bacterially infected cells, or they play an important role in orchestrating an immune response. B cell lymphomas are much more common than T cell lymphomas.[5]

CHRONIC LYMPHOCYTIC LEUKAEMIA

Cancer is the uncontrolled accumulation of abnormal cells. There is an error in the programming of cancerous cells caused by DNA damage that allows them to live indefinitely instead of self-destructing at the end of their normal limited life span. Chronic lymphocytic leukaemia (CLL) is a mostly incurable cancer of B lymphocytes (B cells).

CLL is characterised by the accumulation of mature, clonal B cells (many copies of the same abnormal B cell) in the blood, bone marrow, lymph nodes, and other lymphoid tissues.[1] These leukaemic B cells typically express a protein on their surface called CD5, which is not expressed on healthy B cells.[1] The CLL grow and survive better than normal cells, which means that over time, the clonal B cells begin to crowd out healthy blood cells (e.g., red cells, white cells, platelets) in the bone marrow. When there are large amounts of cancerous cells or not enough healthy blood cells, symptoms of CLL may begin to appear (e.g., fatigue, infections, bruising/bleeding).[6]

CLL is often grouped together with small lymphocytic lymphoma (SLL) because they are considered different versions of the same disease based on current knowledge and technology. CLL and SLL are disorders of the same B cell, and they look the same under a microscope. The difference between CLL and SLL is where the cancer cells predominately collect.[7] In CLL, cancer cells are mostly found in the blood and bone marrow.[7] In SLL, cancer cells are mostly found in the lymph nodes.[7]

The clinical course of CLL is extremely variable.[1] Some people have CLL that grows slowly (indolent) and does not require treatment, while other people have CLL that progresses rapidly (aggressive) and is resistant to treatment.[4,9-11]

For some patients, CLL can change into a faster-growing (aggressive) cancer. This is call Richter's Transformation (RT), and it occurs in approximately 2% to 10% of patients with CLL.[13] Most often, CLL that undergoes RT will present as diffuse large B-cell lymphoma (DLBCL) (approximately 90% of RT cases). If not DLBCL, CLL sometimes transforms into Hodgkin lymphoma (approximately 10% of RT cases).[14] While it is possible for patients with CLL to develop acute leukaemia and myelodysplastic syndrome, it is uncommon.[15]

INCIDENCE

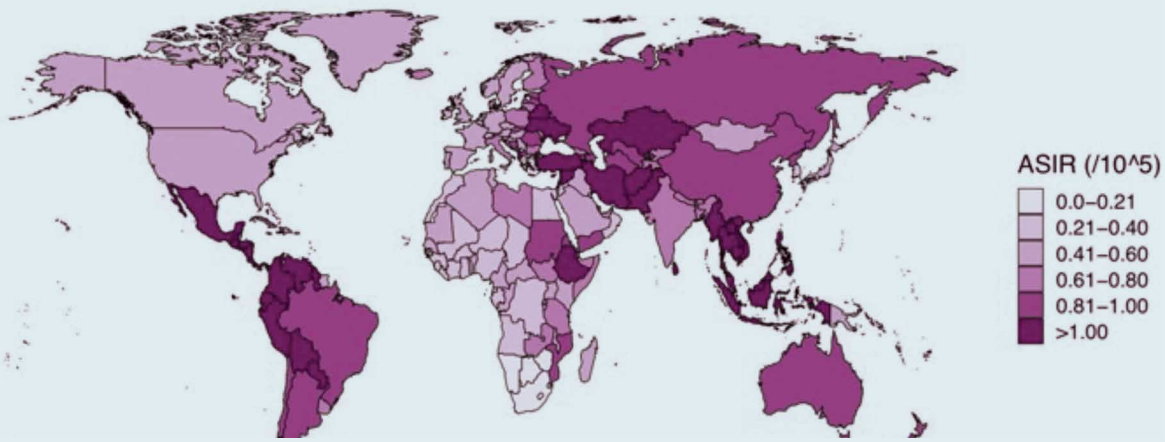
CLL is the most common adult leukaemia in the Western world[1-3,9], accounting for 25-30% of all types of leukaemia.[12]

Males are more commonly affected by CLL than females.[1,3] CLL typically affects older adults; the **median** age of diagnosis is 72 years.[2] Only about 10% of CLL patients are reported to be younger than 55 years.[2] **Because CLL incidence rates rise with age, it is likely the prevalence and mortality of CLL will continue to increase due to the ageing global population.**[1]

A recent study (Dong et al.) used the Global Burden of Disease database to analyse international trends in the **age-standardised incidence rate** (ASIR) of CLL from 1990 to 2017. This study revealed the number of CLL cases globally more than doubled between 1990 and 2017, and most regions experienced a significant increase in the incidence rate of CLL.[16] The greatest increase was observed in East Asia, followed by Southeast Asia and Eastern Europe.[16] At a national level, more than 85% of all countries included in the analysis experienced an increase in CLL incidence between 1990 and 2017.[16] Additionally, the incidence of CLL was markedly higher in developed countries in 2017, with the highest incidences being observed in the United Kingdom, Denmark, and Slovakia (figure 2).[16]

Figure 2. The age-standardised incidence rate (ASIR) of CLL in 2017 (taken from Dong et al.)

ASIR values are shown as 10^5 (values for every 100,000 population). For example, >2.00 means the age-standardised incidence rate of CLL was more than 2 for every 100,000 people in that country in 2017.



SIGNS AND SYMPTOMS

Many people with CLL have no early symptoms and only become aware of the cancer through a routine blood test that detects absolute lymphocytosis (an increase in the number of lymphocytes in the bloodstream beyond the normal range).[3] Approximately 70% of patients present in an early phase of the disease.[14] However, CLL can have a range of presentations with some patients feeling well and being fully active, and others experiencing disease-related symptoms.

Those who do have symptoms may experience[3-4,11]:

- Fatigue
- Unexplained weight loss
- Drenching night sweats
- Feeling of fullness below the ribs due to enlargement of the spleen or liver
- Increased frequency and/or severity of infections
- Easy bruising and bleeding
- Fever (without evidence of infection)
- Enlarged, painless lymph nodes (in the neck, underarm, stomach, or groin)
- Hepatomegaly (abnormal enlargement of the liver)
- Splenomegaly (abnormal enlargement of the spleen)

Approximately 5 to 10% of patients present with typical **B-symptoms**, which are an array of symptoms including unexplained weight loss (more than 10% of body weight), drenching night sweats and fever without a known cause.[3]

RISK FACTORS

Despite extensive research, it is not certain what causes CLL. Recently, it has been reported that the the initiation of the changes underlying CLL may be acquired at the haematopoietic stem cell stage.[1] Haematopoietic stem cells are immature cells found in the bone marrow that can develop into all types of blood cells (e.g., white blood cell, red blood cell, platelets). In the development of CLL, it is suggested that the DNA (genetic material) of a developing haematopoietic stem cell is damaged, causing it to become cancerous and multiply.[1] Research has also shown that CLL can often be initiated by the addition or loss of large amounts of chromosomal material, which can be later followed by additional mutations that make the cancer more aggressive.[1] While the cause of CLL is currently unknown, there are some known risk factors. Risk factors increase a person's chance of developing cancer; however, most do not directly cause cancer.[17] Some people with several risk factors never develop cancer, while others with no known risk factors do.[17]

Risk factors that may increase the risk of chronic lymphocytic leukaemia (CLL) include:

- **Age:** CLL occurs most commonly in older adults, with the median age of diagnosis being 72 years.[2]
- **Sex:** Males are nearly twice as likely to develop CLL compared to females.[15]
- **Race:** Caucasian people are more likely to develop CLL than people of other races.[11]
- **Genetic factors:** Genetic factors play a role in the development of CLL, with a six- to nine-fold increased risk for first-degree relatives of patients with CLL.[2] A family history of other blood and bone marrow cancers affecting B lymphocytes can can also increase a person's risk.[11]
- **Exposure to chemicals:** Exposure to Agent Orange (used during the Vietnam war) has been associated with the development of CLL in some but not all studies.[11,15,18] Beyond this, CLL has generally not been associated with any other environmental or external risk factors.[10]

The management of CLL is determined by the stage and activity of the cancer.

CLL Diagnosis and Pre-Treatment Testing

DIAGNOSIS

A **complete blood count (CBC) with differential** is the usual first step leading to a diagnosis. This routine test is often requested as an element of a check of a patient's general health status. The presence of at least 5,000 abnormal B cells per microlitre of blood (≥5,000 monoclonal B lymphocytes/µl) for at least three months is required to make the diagnosis.[1] However, in practice, if the lymphocyte count is slightly lower and there are other indications that the patient has CLL, clinicians will not wait another three months before retesting.

In 2016, the World Health Organization (WHO) modified its classification of **lymphoid neoplasms**. In 2008, it was unknown if **monoclonal B-cell lymphocytosis** (MBL) was a precursor of CLL. It is now clear that it is and that it precedes nearly all cases of CLL. The updated WHO guideline states that low-count MBL (peripheral blood monoclonal B lymphocyte count of $<0.5 \times 10^9$/L) must be differentiated from high-count MBL. Patients with high-count MBL are recommended to have yearly follow-up; those with low-count MBL rarely develop CLL.[19]

As part of the diagnostic work-up, peripheral blood **flow cytometry** may be used to identify specific proteins that may be on the cell surface, such as CD5, CD19, CD20 and CD23, and to determine whether these cells are clonal. This is called immunophenotyping.[1,6]

Specific diagnostic testing guidelines for CLL produced by the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) can be found in Appendix I.

STAGING

The management of CLL is determined by the stage and activity of the cancer. Two widely accepted clinical staging systems are used to predict patient outcomes.[1] These staging systems use the results of physical examinations and blood counts.[1]

In Europe, the Binet staging system is more widely used, whereas in North America, the Rai staging system is more commonly applied. Both systems recognise the importance of impairment of bone marrow function and define late-stage or high-risk disease through the presence of pronounced anaemia (low red blood cell count) or thrombocytopenia (low blood platelet count). In addition, both the Binet and Rai staging systems divide patients into three groups according to risk (table 1).[1] There is also a modified version of the Rai staging system, wherein the five stages are eliminated, and patients are grouped only by three risk groups (low, intermediate, high) (table 1).[20]

Table 1. Rai and Binet staging systems for CLL[3,20]

Risk Stratification	Rai Stage	Modified Rai Stage	Binet Stage
Low Risk	**0:** High lymphocyte count (lymphocytosis) only	**Formerly stage 0:** High lymphocyte count (lymphocytosis) only	**A:** Less than three areas of lymphoid tissue are enlarged
Intermediate Risk	**I:** Enlarged lymph nodes (lymphadenopathy) only **II:** Enlargement of an organ (organomegaly), usually spleen or liver	**Formerly stages I and II:** Lymphocytosis with enlarged lymph nodes, or enlarged spleen/liver (or both)	**B:** More than three areas of lymphoid tissue are enlarged
High Risk	**III:** Low number of oxygen-carrying healthy red blood cells (anaemia) **IV:** Low blood platelet count (thrombocytopaenia)	**Formerly stages III and IV:** Lymphocytosis with low red blood cell count (anaemia) or low blood platelet count (thrombocytopaenia)	**C:** Low red blood cell count (anaemia) and/or low blood platelet count (thrombocytopaenia)

These clinical staging systems are used for treatment planning. Only patients with active or symptomatic disease, or with advanced Binet (stage C) or Rai (stages III or IV or high risk) stages require therapy.[1] Asymptomatic patients with early- or intermediate- stage cancer (Binet stage A or B; Rai stage 0-II or low/intermediate risk) receive active surveillance care (also called active monitoring or 'watch-and-wait'). This involves closely monitoring a patient's condition without giving treatment unless or until symptoms appear, or until there is evidence of disease progression. Many studies have shown that treating patients with early stage CLL does not result in survival benefit.[1]

Recently, there has been significant progress in CLL therapy, which has made these two clinical staging systems insufficient for classifying certain **prognostic** subgroups.[1] Numerous biological and genetic markers have been identified for CLL. These markers give prognostic information separate from the clinical stage.[1] To account for this, a new prognostic score called the CLL International Prognostic Index (CLL-IPI) was created (table 2). This score includes relevant clinical, biochemical, and genetic information and is a practical approach to treatment recommendation.[3] Compared to the Binet and Rai clinical staging systems, the CLL-IPI more accurately identifies patients who do not require therapy.[1]

Table 2. CLL International Prognostic Index (CLL-IPI) categories[3]

CLL-IPI Category*	Overall Survival at 5 Years	Treatment Recommendation
Low risk (0-1)	93%	Do not treat (active surveillance)
Intermediate risk (2-3)	79%	Do not treat unless the patient is symptomatic
High risk (4-6)	64%	Treat unless the patient is asymptomatic
Very high risk (7-10)	23%	Treat in clinical trial or with non-cytotoxic drugs (no chemotherapy or chemoimmunotherapy)

*CLL-IPI is calculated using 5 prognostic markers that are independent predictors of **overall survival**: age, clinical stage, *TP53* mutation status, IGHV mutation status, and serum β2-microglubulin level

PRE-TREATMENT TESTING

After CLL has been diagnosed, other tests that may have prognostic value and provide an overall idea of the patient's status prior to the start of treatment are conducted. These tests may include:

- Physical exam and medical history
- Genetic and cell protein tests (see next section)
- Imaging (e.g., **PET scan**, x-ray, MRI, ultrasound)
- Comprehensive metabolic panel, that provides information about a body's chemical balance and metabolism
- Hepatitis B testing
- Echocardiogram to check heart function, in select cases
- Measurement of normal immunoglobin levels (for patients who develop repeated infections)
- Bone marrow biopsy

As CLL typically affects older adults, additional recommendations regarding other medical conditions and geriatric assessments should be followed to ensure patients receive the best therapy based on functional status, life expectancy, and predicted treatment tolerability.[21]

While comprehensive geriatric assessment is recommended for patients 65 and older by the NCCN and by the International Society for Geriatric Oncology, there is still no consensus on an optimal validated tool for measuring the comorbidity burden in older patients with CLL.[21]

For a full account of the pre-treatment testing recommended by the iwCLL, please see Appendix I.

PROGNOSTIC GENETIC MARKERS AND CHROMOSOMAL ABNORMALITIES FOR CLL

To help understand the concepts discussed below, please see Appendix II for a description of the biology basics relating to genetic markers, gene mutations, and chromosomal abnormalities.

Genetic Markers

Genes and their associated mutations are used to diagnose cancer and can also be prognostic about how the type of cancer may progress and/or predictive as to how the cancer may respond to available treatments.

The presence or absence of certain mutations can help guide the type of treatment a patient receives and predict how likely the cancer is to respond to certain drugs.

The following gene mutations and protein expressions have been identified in CLL and are currently used to determine best care:

- **IGHV (immunoglobulin heavy-chain variable):** CLL is classified into two subgroups based on whether the CLL cells express a hyper-mutated version of the variable regions of the immunoglobulin heavy chain gene (IGHV).[12] The IGHV gene encodes antibodies that play a role in immune response. The developed of IGHV hypermutation occurs in the process of normal B cell development, specifically, when **naïve B cells** (a B cell that does not yet have a defined purpose) are changing into **memory B cells** (memory B cells provide protection against recurring infections).[12]
  - Patients whose CLL expresses a hypermutated IGHV have a more favourable prognosis than those with unmutated IGHV.
  - Unmutated IGHV is associated with more aggressive disease, which often shows a shorter duration of response to chemotherapy-based treatment.[12]
- ***TP53* (tumour protein 53):** *TP53* is an important tumour suppressor gene.[1] Patients with CLL which carries a mutation of *TP53* have an inferior prognosis and the disease does not respond well to standard chemotherapy.[1,3] This mutation is detected in 4% to 37% of patients with CLL, with lower rates at initial diagnosis and increasing frequency with subsequent disease relapses.[1]

Chromosomal Abnormalities

Identifying chromosomal abnormalities also plays a key role in understanding the prognosis of CLL and the likelihood of the CLL responding to different treatments.

A chromosomal abnormality can be a change in **chromosome** number (gains or losses of entire chromosomes), or a change in chromosome structure (irregular, missing, or extra part of DNA that makes up the chromosome).

There are four chromosomal abnormalities that are most frequently detected in CLL. Approximately 80% of patients with CLL carry at least one of these four abnormalities[22], which include:

1) **17p deletion (del(17p)):** Patients with CLL missing genetic material on the short arm of chromosome 17 are more likely to have an unfavourable prognosis.[3,22] The CLL of patients who carry this deletion is often resistant to traditional chemotherapy and chemo-immunotherapy.[1] This deletion is detected in only 5% to 8% of patients with CLL who have not received chemotherapy, but it becomes increasingly common when the disease recurs after multiple episodes of therapy. A patient may have both del(17p) and del(13q).[1] The 17p deletion nearly always includes the area where a major tumour suppressor gene (*TP53*) is located.[1] However, even if del(17p) is not present, it is still recommended to test separately for TP53 mutation.

2) **11q deletion:** Patients with CLL who are missing genetic material on the long arm of chromosome 11 are more likely to have an unfavourable prognosis if treated with chemotherapy.[3] Some of the poor prognostic features seem to be overcome by the use of chemoimmunotherapy (adding an **anti-CD20 antibody** to the chemotherapy).[1] The 11q deletion is found in approximately 25% of patients with advanced disease stages who have not received chemotherapy, and 10% of patients with early stage disease.[1]

3) **Trisomy 12:** Patients with CLL who have an extra copy of chromosome 12 are more likely to have an unfavourable prognosis when there is a coexisting ***NOTCH1* mutation**.[22] Additionally, trisomy 12 increases the risk of Richter's Transformation, which has a poor prognosis. Trisomy 12 is detected in 10% to 20% of all CLL cases.[1]

4) **13q14 deletion:** Patients with CLL missing genetic material on the long arm of chromosome 13 have a more favourable prognosis (i.e., a more benign course of disease) if the 13q deletion is their only genetic abnormality.[1,22] The 13q14 deletion is the most frequently observed chromosomal abnormality in CLL[12]; it is detected in approximately 55% of all CLL cases.[1]

Beyond these four, another commonly observed chromosomal abnormality in CLL is complex karyotype. Patients with CLL with a complex karyotype have at least three chromosomes which are different from what is considered normal, and may have poorer **progression-free survival (PFS)** and **overall survival (OS)**.[23]

While several diagnostic and prognostic markers have been established for CLL, not all are used in daily clinical practice. Relevant testing for CLL markers suggested in clinical practice guidelines are outlined in Appendix III. Anecdotally, tests for mutations, markers and chromosomal abnormalities are not readily accessible in all countries meaning patients may not receive treatment that is appropriate for their type of CLL.

INITIATING TREATMENT

Not all patients with CLL require treatment when they are first diagnosed. Instead, patients with asymptomatic early or intermediate stage disease are placed in active surveillance where they are re-assessed at one-to-three-month intervals.[3] When the patient's disease progresses or symptoms appear, treatment should be initiated.[1]

The iwCLL guidelines define criteria for symptomatic or active disease. At least one of the following criteria should be met in order to initiate treatment[1,3]:

- Evidence of progressive bone marrow failure with symptomatic anaemia (haemoglobin <10g/dL) or a low platelet count (<100 x 109/L)
- Progressive lymphocytosis
- Enlarged spleen (massive, progressive, or symptomatic)
- Enlarged lymph nodes (massive, progressive, or symptomatic)
- Symptomatic extranodal involvement (e.g., skin, kidney, lung, spine)
- Autoimmune complications (e.g., anaemia, thrombocytopenia) that respond poorly to corticosteroids
- Disease-related symptoms: unintentional significant weight loss, significant fatigue, fevers (without evidence of infection), drenching night sweats

The introduction of new therapy options in recent years has changed the treatment landscape for CLL and improved care for some hard-to-treat prognostic subgroups.

Treatment Overview

Once a patient has met the criteria for treatment, the choice of therapy is the next major decision. Because CLL is rarely cured, the aim of treatment is to reduce symptoms, control the cancer, and extend life.[6]

There are different types of treatment for patients with CLL. Some treatments are standard (currently used in clinical practice) and some are being tested in clinical trials.[4] The main treatment types used for CLL currently include[4,6]:

- Chemotherapy
- Immunotherapy
- Chemoimmunotherapy
- Targeted therapy
- Radiation therapy
- Chemotherapy with bone marrow or stem cell transplant
- Supportive care (sometimes called palliative care) to improve a patient's wellbeing by managing symptoms and side effects (e.g., medications, nutrition, exercise, emotional support, psychotherapies); this is a key part of treatment for all patients, not just those at end-of-life

Within chemotherapy, different kinds of chemotherapy are used depending on the situation. These include **purine analogues** like fludarabine or pentostatin, and **alkylating agents** such as chlorambucil, cyclophosphamide or bendamustine.[3] A patient may receive a purine analogue as part of their therapy if they are in good health and have good kidney function, but if their health is poor, they may receive an alkylating agent without a purine analogue.[6]

Chemoimmunotherapy includes the use of anti-CD20 monoclonal antibodies, immune system proteins made in a laboratory (such as rituximab, obinutuzumab or ofatumumab) in combination with chemotherapy.[3] The antibodies attach to a specific target on cancer cells called CD20. Once attached, the antibodies kill the cells, block their growth, or keep them from spreading.[4] Monoclonal antibodies can sometimes also be used alone without chemotherapy, but this is significantly less effective than their use in combination.

Targeted therapies are treatments that target the **signalling pathways** within a cell that promote the growth and/or survival of CLL cells. **B C cell receptor (BCR) signalling** plays a central role in CLL initiation and disease progression.[8] There are three main classes of drug that can inhibit BCR signalling:

- **Bruton's tyrosine kinase** (BTK) inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib)
- **Phosphatidylinositol 3-kinase** (PI3K) inhibitors (e.g., idelalisib, duvelisib)
- **Spleen tyrosine kinase** (SYK) inhibitors (e.g., fostamatinib)

The **B cell lymphoma 2 (BCL-2) protein** is another target for CLL targeted therapies. BCL-2's role is to promote cell survival and inhibit the action of proteins that would otherwise cause cells to die. BCL-2 is overexpressed in CLL and helps CLL cells survive.[3] Drugs that target this protein (e.g., venetoclax) directly reduce its function, and activate proteins that help with programmed cell death (i.e., killing CLL cells).[3]

A key feature currently directing the choice of therapy in CLL is the presence of either del(17p) (missing parts of chromosome 17) or mutated *TP53* (tumour suppressor gene). As well, in patients who are less fit, the presence of comorbidities and the goal of treatment will play an important role in the choice of therapy.[15]

FIRST-LINE TREATMENT

For the purpose of this review and to determine what treatment protocols should be accessible to patients with CLL, LC reviewed the information from both the NCCN and ESMO clinical practice guidelines for CLL.

In both guidelines, options for first-line treatment are grouped first by whether del(17p) or a *TP53* mutation is present (table 3). The presence of del (17p) and/or *TP53* are associated with decreased survival and impaired response to chemoimmunotherapy.[24] They are among the strongest predictive markers guiding treatment decisions in CLL, hence why the guidelines are organised this way.[24].

For patients who do not have del(17p) or *TP53*, treatment recommendations are further subdivided for 'fit' and 'frail' patients. In the United States, fit patients are generally defined as those under 65 years of age who have a good performance status.

As was earlier noted, another major subgroup classification of patients with CLL is IGHV mutated vs unmutated. Though the NCCN and ESMO treatment guidelines are not organised based on this classification, IGHV mutation status does influence choice of therapy for CLL. Specifically, patients with mutated IGHV are better candidates for chemoimmunotherapy, while patients with unmutated IGHV are more likely to benefit from novel therapy approaches (e.g., targeted therapy).[9]

According to the NCCN guidelines, ibrutinib is the preferred first-line treatment for CLL, especially for older patients.[6] Both guidelines suggest its use for CLL with and without del(17p) or mutated *TP53*. Ibrutinib is a BTK inhibitor, a targeted therapy that blocks Bruton's tyrosine kinase (BTK). This helps stop CLL cells from surviving and multiplying. There are newer BTK inhibitors that may have fewer or different side effects than ibrutinib (like acalabrutinib or zanubrutinib).

In both guidelines, targeted therapies are the preferred treatment for patients who have CLL with del(17p) or mutated *TP53*. Therapies that inhibit BCL-2 and PI3K (as described previously) can be considered, in addition to BTK inhibitors.

For CLL without del(17p) or mutated *TP53*, chemoimmunotherapy is a common treatment, especially for younger fit patients.[2,6] Patients who are younger than 65 years of age and healthy may be treated with fludarabine-based chemoimmunotherapy (e.g., FCR); however, with fludarabine treatment there is a risk of serious infections.[2,6] Bendamustine or chlorambucil combined with a CD20 antibody may be an option as they generally have a more tolerable side effect profile.

There are several **Phase III clinical trials** investigating BTK inhibitors (e.g., ibrutinib) as front-line therapy compared to chemoimmunotherapy. Ibrutinib (alone or in combination with CD20 antibodies) yielded a longer **progression-free survival (PFS**) when compared with fixed duration chemoimmunotherapy (FCR, bendamustine + rituximab , chlorambucil + obinutuzumab) in two Phase III trials.[25-26] However, currently patients need to take ibrutinib until the disease progresses or they have to stop taking the drug due to the impact of the side effects. Another Phase III trial compared ibrutinib plus rituximab versus FCR in young, fit patients and found that an **overall survival (OS)** benefit might exist for those treated with ibrutinib plus rituximab.[27] The final results of these trials may change current practice.

Table 3. CLL first-line treatment recommendations for CLL based on NCCN and ESMO guidelines; therapies written in bold are 'standard of care' first-line therapies

NCCN Clinical Treatment Guidelines (2020)	ESMO Treatment Guidelines (2020)
Without del(17p) or *TP53* mutation - Fit Patient	**Without del(17p) or *TP53* mutation - Fit Patient**
FCR (fludarabine, cyclophosphamide, rituximab)	**FCR (fludarabine, cyclophosphamide, rituximab)**
Bendamustine + rituximab/obinutuzumab	**Bendamustine + rituximab**
Ibrutinib	Ibrutinib
Ibrutinib + rituximab	
Fludarabine + rituximab	
HDMP (high-dose methylprednisolone) + rituximab	
PCR (pentostatin, cyclophosphamide, rituximab)	
Acalabrutinib ± obinutuzumab	
Venetoclax + obinutuzumab	
Without del(17p) or *TP53* mutation - Frail Patient	**Without del(17p) or *TP53* mutation - Frail Patient**
Ibrutinib	Chlorambucil + obinutuzumab
Acalabrutinib ± obinutuzumab	**Venetoclax + obinutuzumab**
Venetoclax + obinutuzumab	**Ibrutinib**
Chlorambucil + obinutuzumab	Acalabrutinib
Ibrutinib + obinutuzumab	
Lenalidomide maintenance (unmutated IGHV)*	
HDMP (high-dose methylprednisolone) + rituximab	
Obinutuzumab monotherapy	
Rituximab monotherapy	
Chlorambucil monotherapy	
With del(17p) or *TP53* mutation	**With del(17p) or *TP53* mutation**
Ibrutinib	**Ibrutinib**
Acalabrutinib ± obinutuzumab	Acalabrutinib
Venetoclax + obinutuzumab	**Venetoclax ± obinutuzumab**
Obinutuzumab monotherapy	Idelalisib + rituximab
Alemtuzumab ± rituximab	
HDMP (high-dose methylprednisolone) + rituximab	
Zanubrutinib (if intolerant to other BTKi)*	

*Therapy not FDA approved for CLL (recommended off-label)

Key
Chemoimmunotherapy
Targeted Therapy
Chemotherapy

TREATMENT RESPONSE

Treatment response is assessed during and at the end of treatment using physical exams and blood tests. There are four types of treatment response[6]:

1) **Complete remission:** No cancer symptoms, blood counts within normal range, enlarged lymph nodes and organs return to normal size and no detectable disease in the bone marrow with routine testing
2) **Partial remission:** Blood counts are returning to normal and the size of enlarged lymph nodes and organs has been greatly reduced or normalised, but there is still some disease present in the bone marrow
3) **Stable disease:** Less than partial remission, the cancer is not getting worse
4) **Progressive disease:** The cancer is getting worse

Sometimes, even if a patient has achieved a complete clinical response (i.e., remission), a very small number of cancer cells can remain in the blood or bone marrow after treatment. This is called minimal residual disease (MRD).[6]

Many studies have found that MRD status (positive or negative/undetectable) has prognostic significance among patients with CLL who achieve a complete or partial response to treatment. Specifically, MRD-negativity is associated with longer progression free survival (PFS) and overall survival (OS).[28-30]

Over the last decade, MRD assessment has been increasingly implemented as a **surrogate end-point** in CLL clinical trials.[31] However, the role of MRD assessment in routine clinical practice has not yet been well defined.[28] There may be a role for MRD-guided treatment approaches in CLL, which may allow for more individualised therapy with better patient outcomes and fewer treatment toxicities.[28] For MRD treatment response assessment or MRD-guided treatment approaches to become clinical realities, the weaknesses that exist in current MRD assessment methods must be eliminated, and more sensitive methods developed that can detect MRD beyond the bone marrow and peripheral blood.[28]

MRD testing methods have to become broadly applicable, accurate, reliable, fast to process and affordable before they can be widely adopted.

SUBSEQUENT TREATMENT

Most treated patients with CLL will develop relapsed disease and require subsequent therapy.[32] Disease relapse is when the cancer returns after it has been in remission for more than six months. When this happens, patients may not require treatment immediately. If treatment is needed, patients may receive the same or a different type of treatment than they were given before.[6] The goal of treatment would be to achieve remission again.

Refractory disease is when the cancer is not in remission at the end of treatment, or when the disease comes back within six months after treatment completion.[6] A different treatment is usually tried in these cases, and good results are often achieved.[6]

Before starting subsequent treatment, the doctor should retest the cancer again to see if there have been any changes in genetic mutations.[31]

For the purpose of this review and to determine which second-line and subsequent treatment protocols should be accessible to patients with CLL, LC reviewed the information from both the NCCN and ESMO clinical practice guidelines for CLL (table 4).

In both guidelines, options for second-line treatment are grouped first by whether del(17p) or a *TP53* mutation is present (table 4). For patients who do not have del(17p) or *TP53*, treatment recommendations in the NCCN guidelines are further subdivided for 'fit' and 'frail' patients. In the ESMO guidelines, treatment recommendations for patients without del(17p) or *TP53* are further divided according to whether the patient's remission was greater or less than 36 months.

Table 4. CLL second-line treatment recommendations for CLL based on NCCN and ESMO guidelines

NCCN Clinical Treatment Guidelines (2020)	ESMO Treatment Guidelines (2020)
Without del(17p) or *TP53* mutation - Fit Patient	**Without del(17p) or *TP53* mutation - Remission > 36 months**
Acalabrutinib	First line chemoimmunotherapy
Ibrutinib	Ibrutinib
Venetoclax ± rituximab	Acalabrutinib
Idelalisib ± rituximab	Venetoclax + rituximab
Duvelisib	Idelalisib + rituximab
Alemtuzumab ± rituximab	
FCR (fludarabine, cyclophosphamide, rituximab)	
Bendamustine + rituximab	
FCO (fludarabine, cyclophosphamide, ofatumumab)	
HDMP (high-dose methylprednisolone) + rituximab	
Lenalidomide ± rituximab	
Obinutuzumab	
Ofatumumab	
PCR (pentostatin, cyclophosphamide, rituximab)	
Zanubrutinib*	
Bendamustine, rituximab + ibrutinib	
Bendamustine, rituximab + idelalisib	
Without del(17p) or *TP53* mutation - Frail Patient	**Without del(17p) or *TP53* mutation - Remission < 36 months**
Acalabrutinib	Ibrutinib
Ibrutinib	Acalabrutinib
Venetoclax ± rituximab	Venetoclax + rituximab
Idelalisib ± rituximab	Venetoclax monotherapy
Duvelisib	Idelalisib + rituximab
Alemtuzumab ± rituximab	
Chlorambucil + rituximab	
HDMP (high-dose methylprednisolone) + rituximab	
Lenalidomide ± rituximab*	
Obinutuzumab	
Ofatumumab	
Zanubrutinib*	
Bendamustine, rituximab + ibrutinib	
Bendamustine, rituximab + idelalisib	
With del(17p) or *TP53* mutation	**With del(17p) or *TP53* mutation**
Acalabrutinib	Ibrutinib
Ibrutinib	Acalabrutinib
Venetoclax ± rituximab	Venetoclax + rituximab
Idelalisib ± rituximab	Venetoclax monotherapy
Duvelisib	Idelalisib + rituximab
Alemtuzumab ± rituximab	Allogeneic stem cell transplant
HDMP (high-dose methylprednisolone) + rituximab	
Lenalidomide ± rituximab	
Ofatumumab	
Allogeneic stem cell transplant	
Zanubrutinib*	

*Therapy not FDA approved for CLL at time of analysis (recommended off-label)

Key

Chemoimmunotherapy
Targeted Therapy
Stem Cell Transplant

Patients who have any of the following features typically do not respond to second-line chemo(immuno)therapy[31]:

- Primary resistance to first-line chemo(immuno)therapy
- Time to disease progression of two to three years after first-line fludarabine-based chemo(immuno)therapy
- CLL cells with del(17p)/*TP53* mutations

Patients with these features should be offered a nonchemotherapy regimen and/or entrance into clinical trials. In some cases (younger, healthy patients), **allogeneic haematopoietic stem cell transplantation** should be considered.[2,31] Currently, there are no **chimeric antigen receptor T-cell (CAR-T) therapies** approved for CLL; however, there are several **clinical trials** occurring.[2]

RICHTER'S TRANSFORMATION

For those patients whose CLL has undergone Richter's Transformation (RT), either into diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL), there are some recommended treatment regimens.

For those with transformed DLBCL, treatment options depend on if the transformed cells are derived from the CLL cells (clonally-related). If the cells are not clonally-related, the cancer will be treated with regimens indicated for DLBCL.[6,14] If the DLBCL has features of being clonally-related to the CLL, a clinical trial is usually offered. However, another option is chemoimmunotherapy with a number of regimens available.[6,14] If chemoimmunotherapy works, patients who are healthy enough might have the option to undergo allogenic stem cell transplant.[14] If the chemoimmunotherapy does not work, patients can receive other recommended treatment-lines for DLBCL. Generally, the DLBCL variant of RT has a poor prognosis because the disease does not respond well to the available DLBCL treatment regimens.[14]

For those with transformed HL, it has a good response rate to the chemotherapy regimen ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Because bleomycin exposure can cause serious pulmonary toxic effects, it can be omitted after two cycles of ABVD if an interim **PET scan** shows a negative **Deauville score**.[14] If the interim PET is positive, escalation to a different chemotherapy regimen called BEACOPP is an option for younger, healthy patients. For older, unfit patients, adding radiotherapy is an option. The HL variant of RT generally has a better prognosis as there is a better response to the available HL treatments.[14]

Therapy Access

To determine the availability of CLL therapies globally, Lymphoma Coalition (LC) looked at access to select chemoimmunotherapy and targeted therapy regimens in LC member countries. Therapies were chosen for inclusion based on current standards of care outlined in the NCCN and ESMO treatment guidelines for CLL. These included:

Chemoimmunotherapy

- FCR (fludarabine, cyclophosphamide, rituximab)
- Bendamustine-rituximab
- Obinutuzumab-chlorambucil

Targeted Therapies

- Ibrutinib (alone and with rituximab)
- Acalabrutinib
- Venetoclax (alone and with rituximab)
- Venetoclax + obinutuzumab

Accessibility was defined as 'therapy being available to a patient through public healthcare'. If a treatment is marked as inaccessible, it means that the therapy is not funded in that country.

Detailed information on therapy access can be found in Appendix IV (by-country and grouped regionally).

When examined regionally (Europe, North America, South America, Asia-Pacific, Middle East, and Africa), though some data could not be found, all of the chemoimmunotherapy regimens appear to be readily accessible across all the regions.

There are a few exceptions, including:

1) Obinutuzumab-chlorambucil is not accessible in Columbia, Uruguay, or South Africa;
2) Bendamustine-rituximab is not accessible in South Africa; and
3) Bendamustine-rituximab is only accessible through special access programs in Czech Republic, Italy, Serbia, Australia, and New Zealand.

Generally, targeted therapies are less accessible across all regions.

The exception is ibrutinib monotherapy (used alone and not in combination with another drug) where New Zealand and South Africa were the only countries where this was inaccessible. Ibrutinib + rituximab as a combination therapy was largely inaccessible in countries where information could be found. This therapy was only accessible in Bulgaria, Germany, Netherlands, the United States, and Singapore. Acalabrutinib monotherapy and venetoclax + obinutuzumab combined therapy were also widely inaccessible across most regions. Many countries within Europe, North America and Asia-Pacific had access to venetoclax monotherapy but fewer have access to venetoclax + rituximab. Lastly, a greater majority of countries in Europe and North America had access to idelalisib + rituximab than countries in South America, Asia-Pacific, or Middle East and Africa.

Access to targeted therapy regimens must be improved globally.

All patients who could benefit from a clinical trial should be able to access one.

Clinical Trials

There is significant clinical trial activity in the CLL space globally. As of January 2021 there were 241 **Phase II** and III clinical trials underway that involve CLL, of those, 133 (55%) are specific to CLL (no other subtypes included).

Research objectives in CLL include the optimisation of first-line therapy (56 trials), but the majority are focused on the development of effective salvage strategies for relapsed/refractory disease (158 trials).

Of the total trials involving CLL, 139 are researching combination therapies. Detailed information is available in Appendix V.

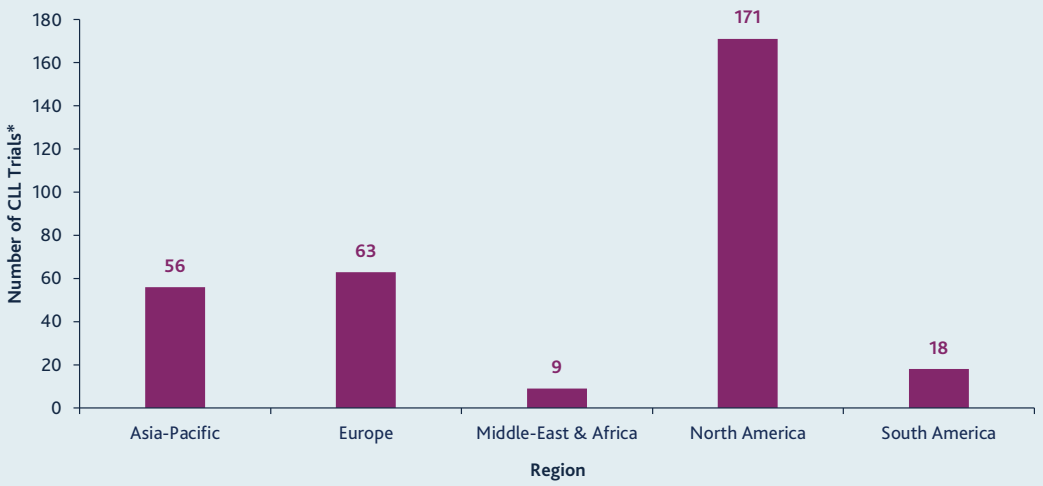
There is a large focus on targeted therapy in CLL, with 84% of trials researching this type of treatment. Only 10% of the CLL-related clinical trials are chemoimmunotherapy-focused.

There are 38 Phase II trials involving **chimeric antigen receptor (CAR) therapies** for patients with CLL; most of these trials are single centre and available only in China or the United States.

LC also examined CLL clinical trial activity by member country (Appendix V). The majority of Phase II and III trials are occurring in the United States (n=169), China (n=34), and Germany (n=29). The following countries have no Phase II or III CLL clinical trials as of this report's writing: India, Singapore, Latvia, Lithuania, Slovenia, Macedonia, Serbia, Uruguay, Venezuela, Barbados, Iraq, Algeria, and Morocco.

When examined regionally (figure 3), North America and Europe have the most CLL-related trials occurring, while South America and the Middle East and Africa have the least. Out of the 171 clinical trials occurring in North America, only two occur outside of the United States. Additionally, when Europe is examined by-country, there is a large disparity in the trials underway in Western versus Eastern Europe. **Compared to Western Europe, there are far fewer Eastern European countries with available trials, and a lower number of trials available within these countries.** Other such by-country disparities exist across the regions. For instance, 34 of the 56 clinical trials in Asia-Pacific are in China.

Figure 3. Number of CLL-related clinical trials occurring by-region



*The number of trials per region will not equal the sum of the trials per country listed under that region in Appendix V (Table 2), as many trials occur in more than one country

Given that CLL typically affects older adults, it is important that CLL clinical trials be designed to include older patients. There are many investigators interested in the treatment of cancer in older patients; however, it was not until recently that clinical trials in CLL began to focus on the older and less fit populations.[33] There is still variability among CLL clinical trials in terms of if they include and/or encourage the enrollment of older patients.[33] It is important that clinical trials match the age of the typical patient in order to more accurately predict how the therapy will perform and affect patients in the real world. Of the 133 CLL-specific clinical trials identified, 84% had no age requirements other than being 18 years and older. There were six clinical trials that had eligibility exclusively for patients aged 65 years and older. Fifteen clinical trials had age limits for participation (i.e., patients over a specified age cannot participate), which ranged from 65 years to 90 years.

There are several barriers that must be addressed to facilitate the participation of older patients in CLL clinical trials.

- Clinical trials must be made more accessible, both geographically (e.g., some older patients are less likely to travel to tertiary centres for care), and in terms of the number of hospital/clinic visits required.
- Many clinical trial designs inadvertently exclude patients with physiologic aging due to strict requirements (e.g., organ function). There is a continued need to embed function status and frailty assessments in clinical trial designs; however, the inclusion of strict organ function requirements in clinical trials should be thoroughly thought through, and only implemented where wholly justified. Reducing some of these organ function requirements might allow the enrollment of patients that more closely mimic the CLL population at-large.

CLL is associated with significant immune suppression, comorbidities, and advanced age, all of which act as compounding risk factors for Covid-19 infection.[37-39]

Covid-19 Considerations for Patients with CLL

Coronavirus disease 2019 (Covid-19) was first detected in Wuhan, China in December 2019.[34] Coronaviruses are a family of viruses that can cause mild illness, like the common cold, to more severe diseases, like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[35] Covid-19 is characterised by rapid human-to-human transmission and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020.[36]

COVID-19 AND CLL

Patients with cancer are more susceptible to Covid-19 not only because of their malignancy, but also because of their anti-cancer therapies (e.g., chemotherapy, targeted therapy, immunotherapy) that may result in a suppressed immune system.[34] Patients with CLL may be at particularly high risk for Covid-19 infection. CLL is associated with significant immune suppression, **comorbidities**, and advanced age, all of which act as compounding risk factors for Covid-19 infection.[37-39]

Accumulating evidence also suggests that patients with cancer are at higher risk for a more severe course of Covid-19 once contracted.[41] Research has shown that compared to the general population, patients with CLL have an inferior immune response to Covid-19.[40] This means that they develop antibodies (anti-SARS-CoV-2 IgG) that help fight off the virus at a slower rate, and therefore might have a more severe disease course.[40]

Two recent studies have shown that patients with CLL experience more complications, morbidities, and higher mortality rates due to Covid-19 than the general population (table 5).

Patients who undergo chemoimmunotherapy are likely to be at increased risk for clinical complications following Covid-19 infection.[37] In contrast, BTK inhibitors (e.g., ibrutinib, acalabrutinib) may have a protective effect and this is being explored in clinical studies with conflicting results.[37] For example, in table 5, the Mato et al study found that overall survival from Covid-19 was not affected by CLL treatment (mostly ibrutinib), whereas the Scarfò et al study found that ibrutinib had a protective effect.

Table 5. Studies examining the associated risks of Covid-19 for patients with CLL

Study	Study Population	Key Results
Scarfò et al. 2020[38]	Patients with CLL with confirmed Covid-19 diagnosis (n=190)	79% of patients presented with severe Covid-19 symptoms (requiring oxygen and/or intensive care admission). Severe Covid-19 was associated with advanced age (≥65 years). 40% of those with severe Covid-19 were receiving treatment or had received treatment in the past 12 months. 55% of patients with severe Covid-19 died versus only 2.6% of those with mild disease; age and comorbidities did not impact mortality. Hospitalisation rate for severe Covid-19 was significantly lower for patients on ibrutinib versus those on other treatments (or off treatment). **Doi:** doi.org/10.1038/s41375-020-0959-x
Mato et al. 2020[39]	Patients with CLL diagnosed with symptomatic Covid-19 (n=198); 39% of patients had no previous CLL treatment	Hospital admission occurred in 90% of patients with CLL due to COVID-19. 45% (n=90) of patients were receiving treatment at the time of Covid-19 diagnosis, most commonly BTK inhibitors (n=68). At a median follow-up of 16 days, the overall case fatality rate was 33%, and 25% remained admitted. Untreated and treated cohorts had similar rates of hospital admission (89% vs 90%, respectively), intensive care unit admission (35% vs 36%), **intubation** (33% vs 25%), and mortality (37% vs 32%). CLL treatment with BTK inhibitors at Covid-19 diagnosis did not impact survival. CLL patients admitted with Covid-19, regardless of disease phase or treatment status, were at a high risk of death. **Doi:** doi.org/10.1182/blood.2020006965

The clinical outcomes of Covid-19 infection in patients with untreated CLL remains an important area of research.[37]

MANAGING PATIENTS WITH CLL DURING COVID-19

Experts have developed protocols describing how to manage patients with CLL during Covid-19. Some of the general recommendations include[42]:

- Limiting patients' exposure to potential Covid-19 infection by minimising the number of hospital/clinic visits, postponing in-hospital routine follow-up appointments, and substituting them with remote check-ins
- For patients in need of treatment, it is recommended to postpone the initiation of therapy, if possible, until the pandemic trajectory is decreasing
- When treatment cannot be further deferred, it is recommended to use the therapy that requires fewer clinic visits and/or is less immune suppressive (e.g., using BTK inhibitors instead of anti-CD20 monoclonal antibodies)
- Test asymptomatic patients for Covid-19 seventy-two (72) hours before treatment
- Postpone therapy until recovery from infection in those patients with CLL on treatment who have contracted Covid-19

At this time, there is no consensus on a standard protocol for the management of patients with CLL during the pandemic, nor is there a general agreement on the best treatment protocol for patients with CLL who are diagnosed with Covid-19.[40]

COVID-19 VACCINATION AND TREATMENT

CLL is associated with impaired **humoral response** to vaccination.[37,43] This means that the immune systems of patients with CLL, due to their disease or its treatment, are not good at making antibodies or mounting an immune response to existing vaccines.

A growing number of patients with CLL have long-term exposure to treatments that directly affect the immune system through depleting a patient's B cells, which are necessary for making antibodies ('humoral immunity'). This can further reduce a patient's ability to respond to vaccination.[43]

It is important to remember the immune system has two responses to an **antigen**. One is to make and keep making antibodies to the antigen. This process creates a large burst of antibody aimed at destroying the antigen that gradually lessens as time goes on. The second is the development of memory cells whose role is to rapidly respond to a further encounter with the same antigen. It is possible for a small amount of antibody to be made (i.e., a poor humoral response) but immune memory response be very strong.

There is no evidence to suggest that Covid-19 vaccines are less safe in patients with blood cancer, though Covid-19 clinical trials have admittedly included few cancer patients.[46] LC encourages patients with CLL to discuss Covid-19 vaccine options with their healthcare teams.

Targeting **'passive immunity'** in Covid-19 vaccine research is potentially a good approach for helping those who are less likely to benefit from vaccinations due to being immunocompromised. Passive immunity means that a person is given antibodies to a disease rather than producing them through their own immune system.[44]

This is what is being explored in long-acting antibody (LAAB) trials. If a patient is given these antibodies, it should prevent the virus from entering their cells and infecting them or reduce the risk of severe Covid-19 if they are infected. If the antibodies work as promised, they should give protection for at least six months, without the patient's immune system ever having to learn how to make the antibodies itself.[45] This 'immune booster' approach may be a viable option for immunocompromised patients (with CLL and otherwise).[45]

It is crucial that patients with CLL be eligible to receive Covid-19 vaccinations to reduce the risk or severity of Covid-19 infection. They should also receive priority access to any newly developed antivirals and treatments for Covid-19.

It is important to understand the patient experience and their quality of life, from diagnosis through to the point they are no longer experiencing effects from their disease or any adverse effects from treatment.

The Patient Experience

It is important to understand the experience of patients with CLL and their quality of life, from diagnosis through to the point they are no longer experiencing effects from their disease or any adverse effects from treatment. LC conducts a global survey of patients every two years that is distributed within the patient community. Through this survey, the impact of diagnosis, treatment and care can be better understood, and LC and its global members can bring the patient voice forward.

The LC 2020 Global Patient Survey on Lymphomas & CLL (GPS) results are used in this report to provide a sense of the experience of patients with CLL and SLL.

The LC 2020 GPS received 11,878 responses, including 9,179 patients and 2,699 caregivers. There was representation from respondents in over 90 countries around the world, of which **1,774 were identified as patients with CLL/SLL** (19% of the total patient respondents).

Patients were asked questions about their understanding and awareness (including guidance and support), symptoms and treatment side effects, psychosocial concerns, communication with the doctor, and barriers to care.

UNDERSTANDING AND AWARENESS

When asked about their initial diagnosis experience, 89% of patients said they clearly understood they were being diagnosed with cancer but one in four were not told the specific subtype.

Two-thirds of patients reported not knowing if any genetic and biologic markers applied to them (table 6).

Understanding the characteristics of CLL/SLL is key given its chronic nature as well as its **heterogeneity**. If patients do not have a good understanding about their subtype and the chromosomal alterations associated with CLL/SLL, they are unable to seek the correct information that applies to their disease and will help them be better informed.

Table 6. Genetic and biologic markers that patients reported as applicable to their CLL/SLL

Genetic or Biologic Marker	%
IGHV mutated	8%
IGHV unmutated	10%
13q14 deletion	9%
11q23 deletion	4%
17p deletion	6%
Trisomy 12	4%
TP53 mutated or missing	4%
Other	5%
I do not know	66%

*Patients were able to check all that apply, percentages will not add to 100%

Patients were asked whether they received and understood information on various topics around the time of diagnosis (table 7). While the majority of patients were given information about each topic, in all cases, less than half of patients reported completely understanding this information. Further, a fifth of patients were not given information on the process and stages of their care (21%) or on managing treatment side effects (20%).

Table 7. Information that patients were given at diagnosis and how well they understood it

Information Topic	Yes + Understood Completely (%)	Yes + Understood a Little (%)	Yes + Did Not Understand (%)	Not Given Information (%)
Information on different treatment options (including active surveillance)	41%	41%	4%	14%
Information on process and stages of care	37%	37%	5%	21%
Information on how to manage treatment side effects*	38%	37%	5%	20%

*This question was not asked to patients who had never received treatment

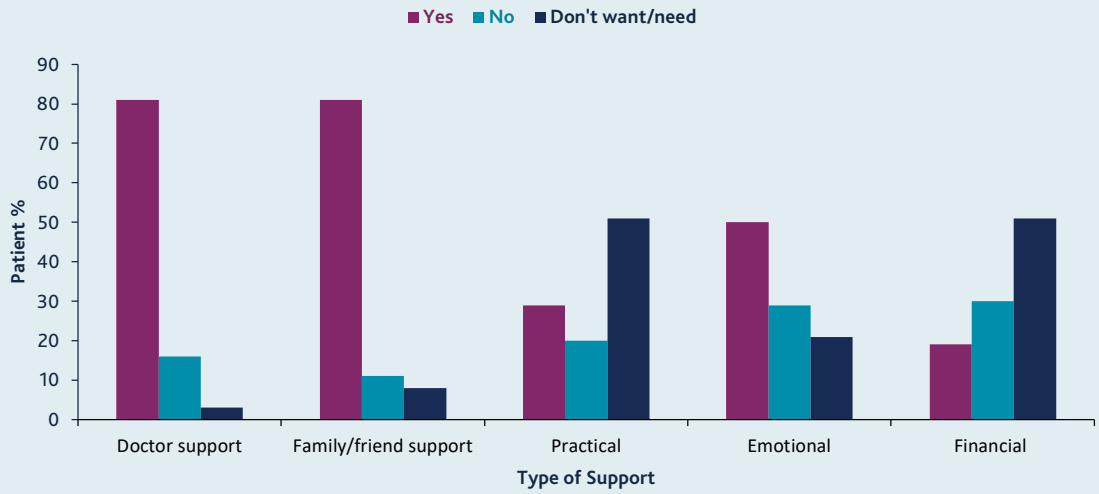
Though three in five patients said they received the right amount of information at diagnosis, a third reported not receiving enough. Most patients had the greatest need for information within the first month following diagnosis (52%). They wanted more information about their diagnosis and what is means (56%), treatment options (55%), and treatment side effects (33%).

Patients reported that their primary sources for information were doctors, websites, and patient organisations.

Most are confident in their ability to get the information they need from their doctor (83%) and are confident they can find reliable information about their CLL/SLL (75%). Access to credible, timely information is an important factor in a successful patient experience. It is critical that all parties work together to meet this need and provide patients with the information and support they need, right from the beginning of their experience.

The majority of patients reported receiving enough general support from doctors (81%) and from family/friends (81%) throughout their experience. However, only half (50%) received enough emotional support, and less than a third received enough practical or financial support (figure 4).

Figure 4. Did patients receive enough support throughout their experience in various areas?



Patients were asked a series of questions about their role in healthcare decision-making. Most patients (90%) are involved as much as they want to be in decisions about their care.

- More than 75% of patients agreed or strongly agreed that they have good conversations with their doctor about their care and treatment plan (77%), seek clarification when they do not understand (91%), are confident in communicating concerns to their doctor (84%), and are confident in their ability to positively impact their health (78%).
- 82% say they always understand their doctors' advice and treatment plans.
- For those in treatment (or who had been treated in the past), almost a third (31%) had talked to their doctor about wanting to change their treatment to better meet their needs within the last two years, but only 3% of these patients chose a treatment that was not recommended by their doctor. 30% of patients got a second opinion about their most recent treatment.

However, more than a quarter of patients (28%) agreed or strongly agreed that they feel overwhelmed by managing their health and condition.

Patients were asked how confident they felt in managing their health problems day-to-day (if they had health problems) (figure 5). Less than a third reported feeling very confident, and 12% reported not feeling confident (not very or not at all).

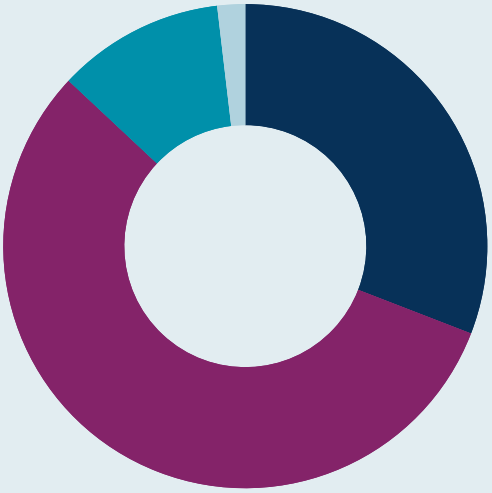
Figure 5. How confident patients felt managing health problems day-to-day

Very confident **31%**

Fairly confident **56%**

Not very confident **11%**

Not at all confident **2%**



When asked more specific questions about managing their condition on a daily basis:

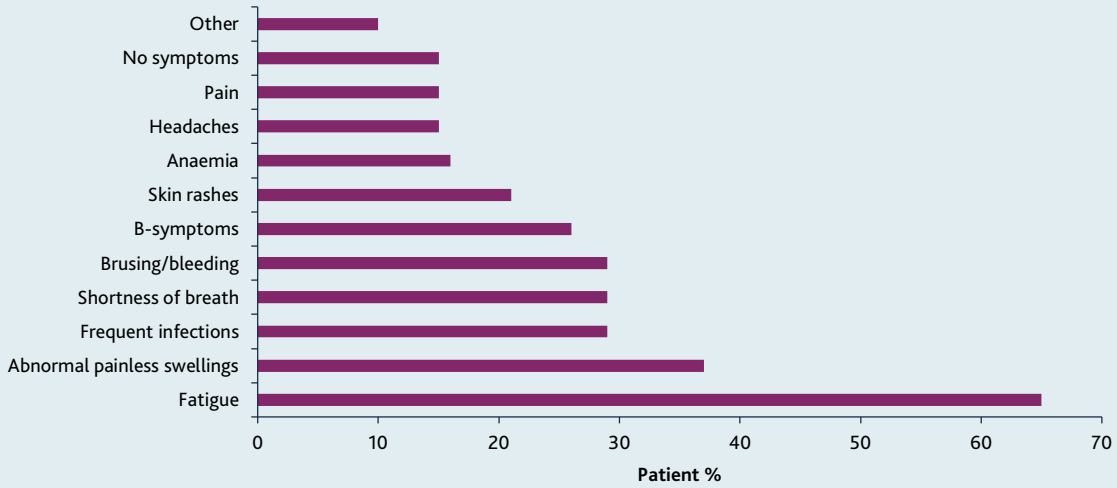
- 77% of patients that have received treatment agreed or strongly agreed that they know what their prescribed medications do
- 97% of those in treatment (or who had been treated in the past) agreed or strongly agreed that they understand how to take their medications at home
- 81% of patients agreed or strongly agreed that they make the recommended lifestyle changes for their disease.

However, 30% of patients agreed or strongly agreed that they wait until health issues cannot be ignored before seeking help, and 16% disagreed or strongly disagreed that they are confident in their ability to keep their side effects from interfering with what they want to do.

CLL SYMPTOMS AND TREATMENT SIDE EFFECTS

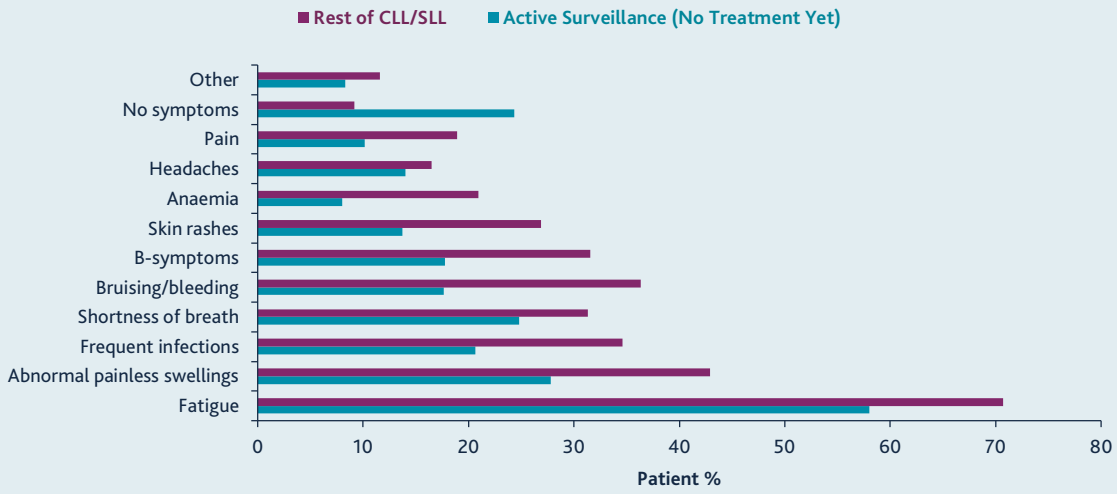
Patients were asked to identify any symptoms of CLL/SLL they had experienced (figure 6). The top five reported symptoms were fatigue (65%), abnormal painless swellings (37%), and frequent or repeated infections, shortness of breath, and bruising/bleeding (29% each).

Figure 6. Symptoms of CLL/SLL that patients reported experiencing



This trend holds true when comparing those in active surveillance who have never been treated (734 of the 1,774 total responses) with those who have been treated (figure 7).

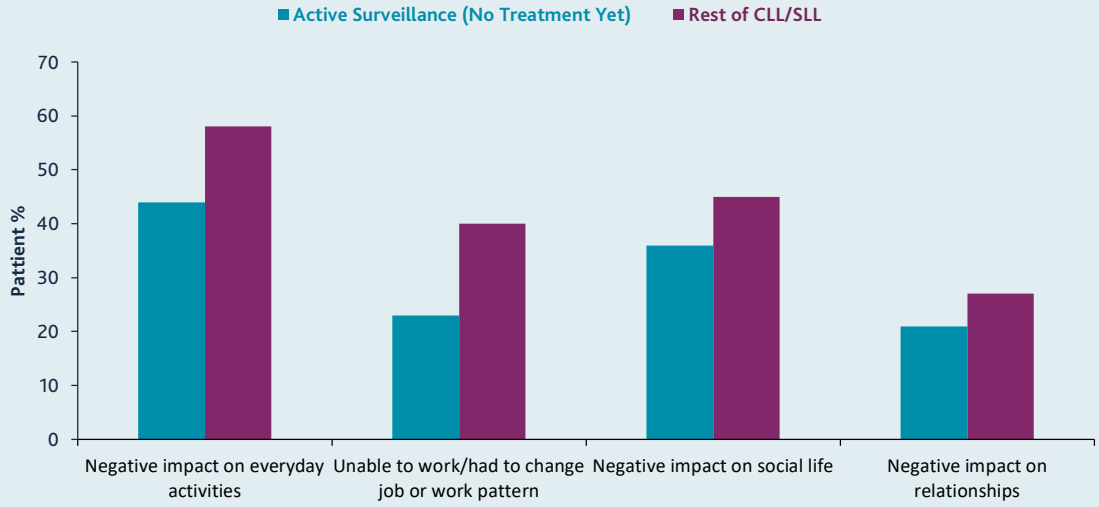
Figure 7. Prevalence of CLL/SLL symptoms among patients in active surveillance (no treatment yet) versus the rest of the CLL/SLL population



Though fewer patients in active surveillance reported CLL/SLL symptoms, at least 8% of these patients reported experiencing each symptom (ranging up to 58% for fatigue). This signals that despite not requiring treatment, these patients may require support to manage these symptoms.

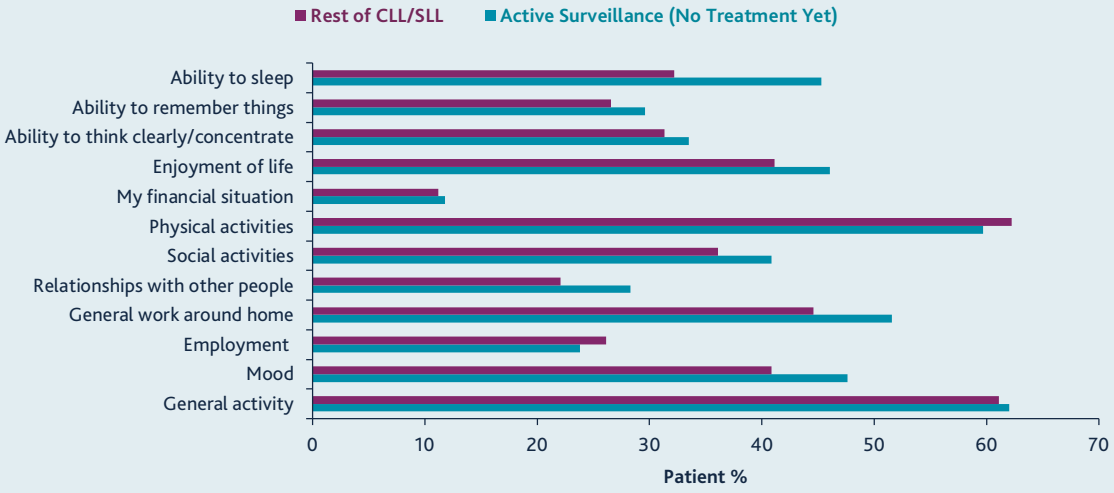
This is further confirmed when examining how CLL/SLL symptoms impacted well-being (figure 8). Though a lesser proportion of those in active surveillance reported each impact category (compared to the rest of CLL/SLL patients), more than a fifth of those in active surveillance did report experiencing each impact.

Figure 8. How CLL/SLL symptoms impacted well-being among those in active surveillance (no treatment yet) versus the rest of patients with CLL/SLL



Fatigue was a major concern for all patients with CLL/SLL, regardless of if they had been treated or not. Fatigue has a massive impact on many patients' quality of life. Those in active surveillance reported a greater burden of fatigue across most areas of life (figure 9).

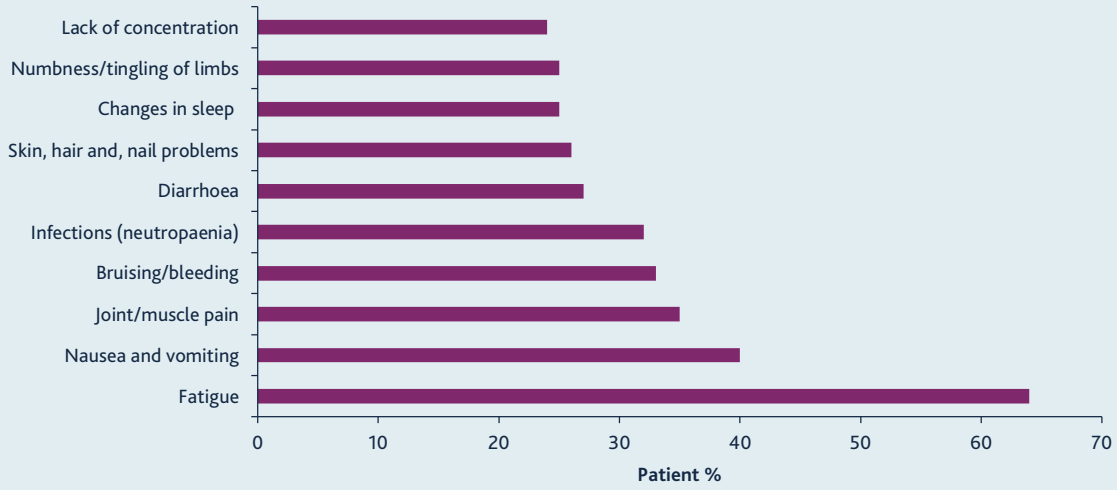
Figure 9. Reported impact of fatigue on quality of life among those in active surveillance versus the rest of patients with CLL/SLL



Understanding cancer-related fatigue and the repercussions it may have for patients before, during, and post treatment is an important factor that must be addressed.

Patients who were in treatment, or who had been treated in the past, were asked which treatment-related side effects they had experienced. The top ten reported side effects are shown in figure 10. Patients were most commonly treated with chemoimmunotherapy (48%) and targeted therapy (32%).

Figure 10. Top ten treatment-related side effects that patients with CLL/SLL (in treatment or received treatment in the past) reported experiencing



The medical issues (figure 10) reported by patients with CLL/SLL are commonly reported treatment-related side effects, **highlighting the continued need for better treatment options with fewer toxicities. When patients were asked to rank the importance of outcomes relating to treatment, 'a cure' ranked first (58%), but 'quality of life' (45%) and 'fewer side effects to tolerate' (45%) ranked second and third, respectively.**

Additionally, except for nausea and vomiting (mostly experienced while in therapy), each of the top treatment-related side effects were reported for eight or more years by at least 7% of patients who experienced them (table 8). Nearly a fifth (17%) of those who experienced fatigue reported experiencing it for more than eight years.

Side effects can impact quality of life and well-being. The majority of patients (60%) who experienced treatment-related side effects reported that their everyday activities were negatively impacted as a result: 38% were unable to work or adjusted their working pattern; 44% reported that their social life was negatively impacted; and 23% reported a negative impact on relationships.

Table 8. How long the top five treatment-related side effects were experienced by patients with CLL/SLL

	Number of Years Experienced (Patient %)					
Treatment-Related Side Effect	**>1 %**	**1-2 %**	**2-5 %**	**5-8 %**	**<8 %**	**DK/CR* %**
Fatigue	20	23	26	11	17	3
Nausea and vomiting	83	6	4	1	1	5
Joint/muscle pain	31	29	23	9	7	1
Bruising/bleeding	24	27	27	10	9	3
Infections	30	24	20	9	14	3

*DK/CR: Don't know/can't remember.

PSYCHOSOCIAL CONCERNS

Psychosocial effects encompass the psychological and emotional well-being of the patient and how it impacts their day-to-day life. The chronic nature of CLL/SLL means all patients require more support to manage the coupled long-term psychosocial issues that impact well-being.

For this section, we again compared those patients in active surveillance (no treatment yet) (n=734) against the rest of the CLL/SLL population (n=1040).

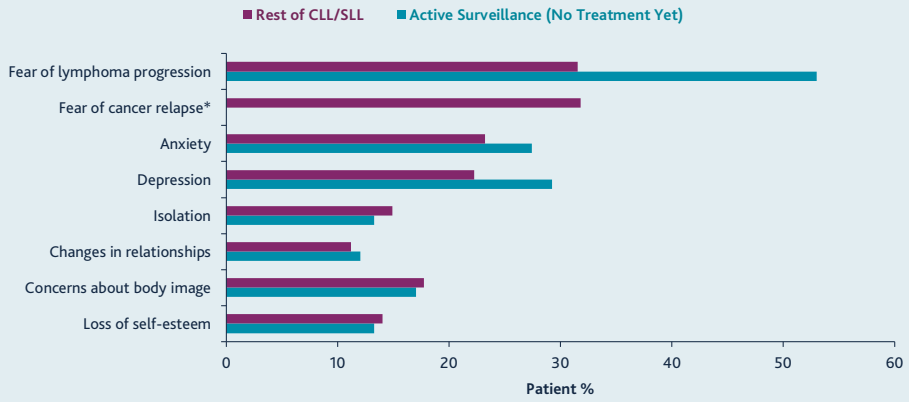
Patients with CLL/SLL may spend several years living with the disease without treatment. More than a third (36%) of patients reported being in active surveillance (without treatment) for more than five years. Many patients live in constant fear of disease progression. Additionally, if active surveillance is not well explained and understood from the outset of diagnosis, it may seem like a risky or passive approach to a serious disease. All these factors can lead to a great deal of distress for patients.

Compared to the rest of the CLL/SLL population, a greater proportion of patients in active surveillance reported experiencing fear of lymphoma progression, anxiety, and depression (figure 11). Patients in active surveillance require more support for these specific issues, as well as ongoing reassurance that their symptoms are being actively monitored and that treatment will begin when necessary.

Despite certain issues being more prevalent among those in active surveillance, more than 10% of patients in both groups reported experiencing each psychosocial issue (figure 11). Fear of progression/recurrence, anxiety, and depression were high (<20%) in both groups. To note, patients in active surveillance were not asked if they experienced fear of cancer relapse as they had not yet been treated.

In supporting patients with these psychosocial issues, something that must be considered currently and going forward are the exacerbating effects of Covid-19. **CLL/SLL diagnosis and treatment (including active surveillance), compounded by being high risk for COVID-19 infection and complications, can create high levels of psychological distress for patients (e.g., anxiety, depression).** Additionally, patients with CLL/SLL during Covid-19 must manage stress related to less frequent touchpoints with their care team, potential treatment changes and/or delays, and the absence of traditional support systems due to social distancing protocols. Improved psychosocial supports must be designed with these factors in mind.

Figure 11. Psychosocial issues experienced by patients in active surveillance (no treatment yet) compared to the rest of patients with CLL/SLL



*Patients in active surveillance were not asked about fear of relapse.

PATIENT-DOCTOR COMMUNICATION

In previous years, the LC GPS has shown that patients are more likely to communicate their medical issues with their doctors than their psychosocial issues. Additionally, when patients do communicate psychosocial concerns, they are often not met with adequate support from their healthcare providers.

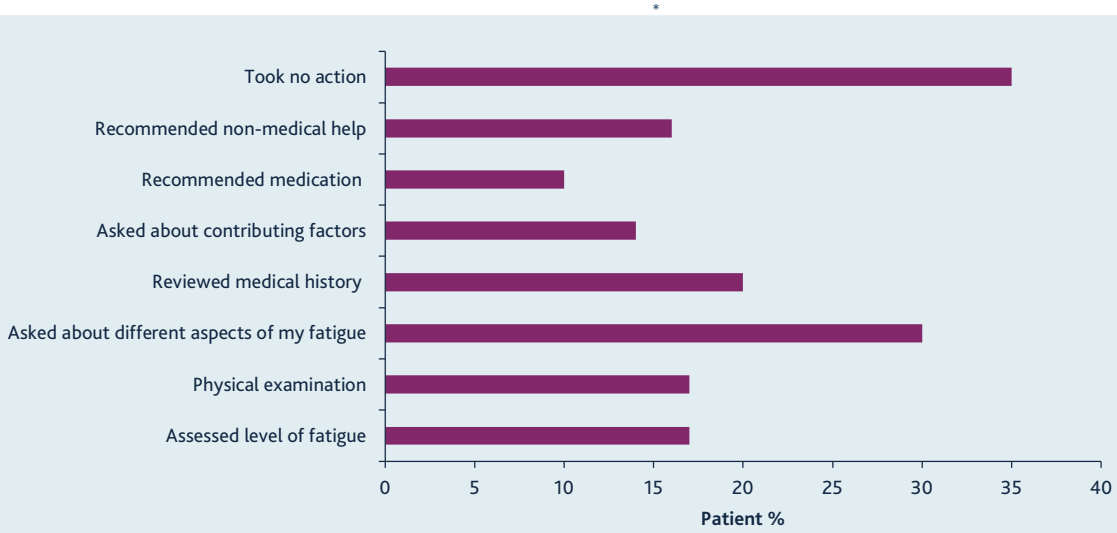
In the LC 2020 GPS, nearly all patients with CLL/SLL (96%) who experienced treatment-related side effects reported discussing them with the doctor, of which 77% reported being helped (either definitely or to some extent). Patients who were helped by their doctors reported receiving medication (64%), being provided with further information (39%), and/or being referred to another source of support (15%).

Though fatigue was the top reported symptom and treatment-related side effect, compared to discussing treatment side effects generally, fewer patients who experienced fatigue reported specifically discussing it with their doctor (74%). Of those who did not discuss their fatigue, the top reported reasons for not doing so were believing nothing could help (32%), thinking they could handle it on their own (31%), and/or that the doctor never started a discussion about it (22%).

Patients who discussed their fatigue with their doctor were asked how the doctor helped (figure 12). More than a third (35%) of patients reported that the doctor took no action after their discussion. Less than a fifth of patients reported that the doctor assessed their level of fatigue (17%), did a physical examination (17%), or asked about any contributing factors (14%).

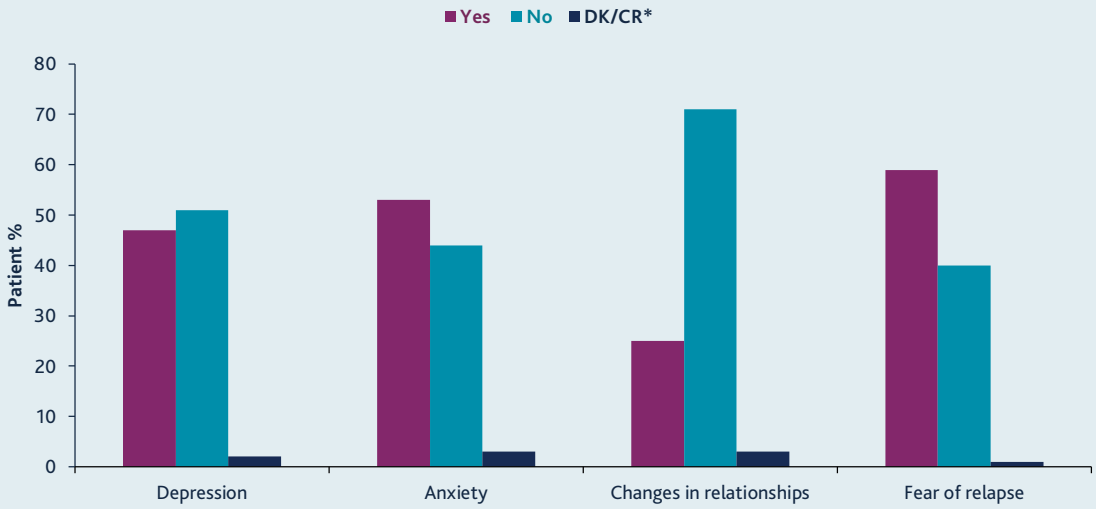
All of the actions listed in figure 12 are taken from clinical practice guidelines (NCCN/ESMO) for cancer-related fatigue, all of which should be routinely implemented when a patient presents with fatigue. Additionally, only 17% of patients reported the doctor definitely followed-up with them about their fatigue. This represents a major gap in the care of patients with CLL/SLL.

Figure 12. Actions that doctors took after patients with CLL/SLL discussed fatigue with them



As in past years, there was significantly less communication about psychosocial issues to the doctor. In the LC 2020 GPS, there was a focus on four issues for further questions about communication, including: depression, anxiety, changes in relationships, and fear of cancer relapse. Of patients who reported experiencing these issues, less than 60% reported discussing any of them with their doctor (figure 13).

Figure 13. Did patients discuss psychosocial issues that they experienced with their doctor?

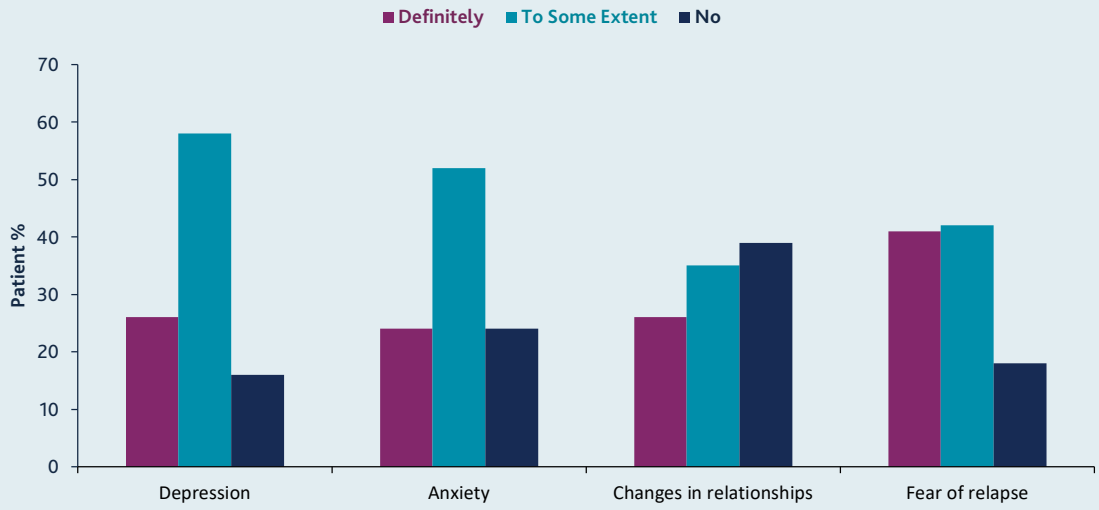


*DK/CR: Don't know/can't remember

Of those who did not discuss these issues, the top reported reasons for not doing so were thinking they could handle it on their own, not thinking the issue was a big deal, and/or not wanting to bother the doctor.

Of those who did discuss these issues with the doctor, in all cases, patients reported the doctor was only able to help to some extent than definitely help (figure 14). For changes in relationships, most patients reported the doctor was not able to help.

Figure 14. Was the doctor able to help if patients discussed the issue with them?



Less than 40% of patients who discussed these issues reported that their doctor definitely followed-up with them about it (depression 30%; anxiety 28%; changes in relationships 24%; fear of relapse 36%).

It is clear that a communication gap still exists surrounding psychosocial concerns; the two-way exchange of information between patients and their doctors continues to be impaired.

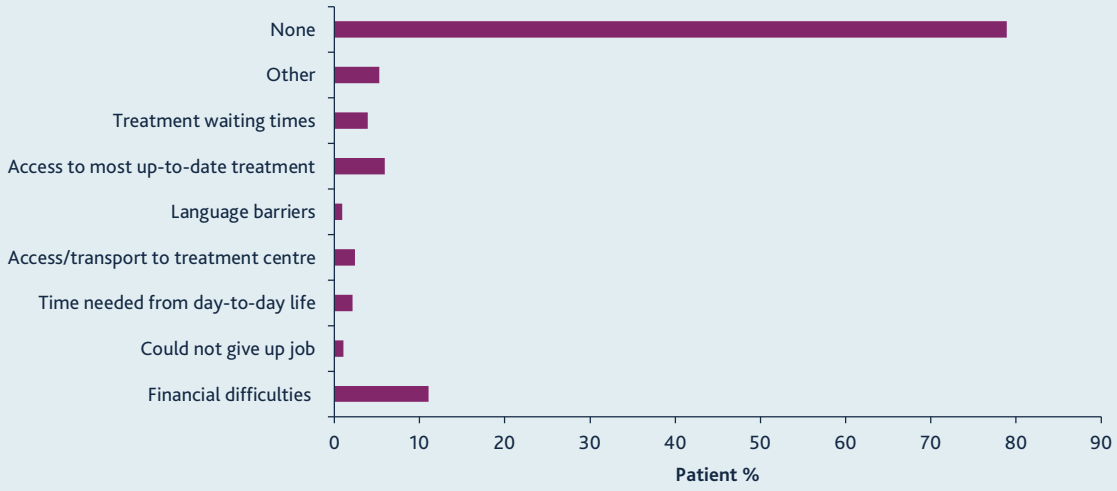
To encourage communication, the emotional impact of a cancer diagnosis must be acknowledged at the outset, and the emotional cues from the patients must be recognised and responded to throughout their experience. Additionally, it is imperative that physicians be educated on the importance of early access to emotional support for patients and be provided with the information on how to find these resources.[47]

Healthcare providers cannot be expected to provide all the information and support patients need; however, patients must be directed to the appropriate resources. This can include other resources that are hospital or community-based, as well as patient organisations. There continues to be room for improvement here as less than 40% of patients reported being directed to another source of support by their doctor for any psychosocial issue.

BARRIERS TO CARE

There are many reasons why a patient may not be able to access treatment. The two main barriers reported by patients with CLL/SLL were financial difficulties (11%) and access to the most up-to-date treatment (6%). However, the majority of patients reported not experiencing any barriers to treatment (79%) (figure 15).

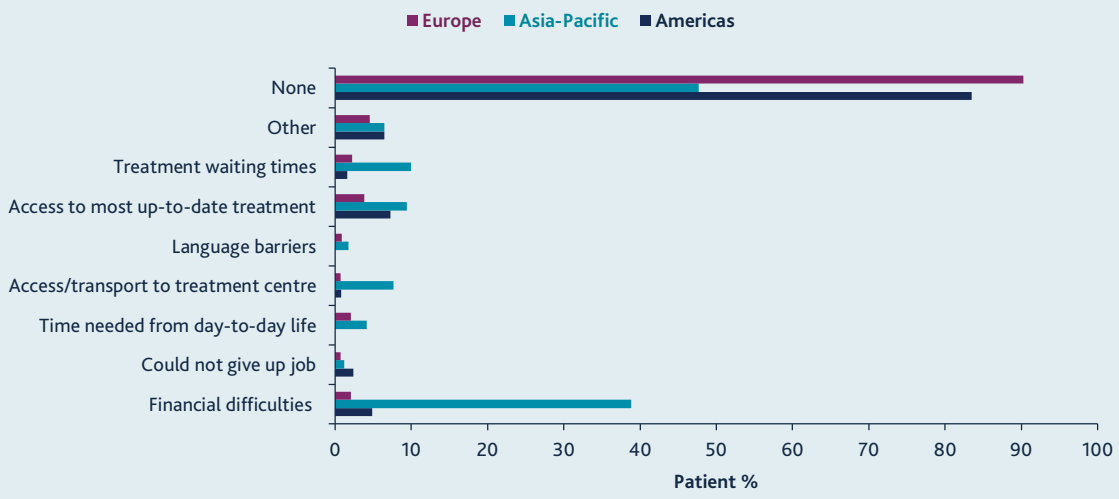
Figure 15. Barriers to treatment that patients with CLL/SLL reported experiencing



When examined regionally, it is apparent that barriers to care are most prevalent in Asia-Pacific (figure 16). Less than half of patients (48%) in Asia-Pacific reported experiencing no barriers to treatment, compared to 83% in the Americas and 90% in Europe.

The most reported barrier to treatment in Asia-Pacific was financial difficulties (39%), which was only reported by 5% of those in the Americas and 2% of those in Europe. This could be partially attributable to the 'out-of-pocket' healthcare systems that exist in many Asian countries. These systems create high stress and have large financial impacts for patients; many middle-class households in Asia face impoverishment after paying for cancer care.[48]

Figure 16. Barriers to treatment reported by patients with CLL/SLL regionally (Middle East/Africa excluded due to low response)



The most reported barrier to treatment in the Americas and in Europe was gaining access to the most up-to-date treatments (figure 16). The most up-to-date treatments are often accessed via clinical trials. In clinical practice guidelines for treating CLL/SLL (e.g., NCCN, ESMO), clinical trials are recommended for certain patients with CLL/SLL in both first- and second-line therapy settings. However, when patients were asked if they were currently or had ever been in a clinical trial for their CLL/SLL, 82% said 'no'. When examined regionally, the greatest proportion of patients in Asia-Pacific had been (or were currently) involved in a clinical trial (Asia-Pacific 22%; Americas 20%; Europe 16%). Never being presented with an opportunity to take part was the most cited barrier to clinical trial participation globally (66%), and across the regions (Asia-Pacific 61%; Americas; 62%; Europe 69%).

Conclusions and Recommendations

It is likely that the prevalence and mortality of CLL will continue to increase because the global population is ageing. Therefore, it is important for major gaps in understanding, treatment, and care to be addressed.

Lymphoma Coalition firmly believes that if we, patient organisations, and other key stakeholders work together, we can jointly bring about positive change. Change will take time. There are steps we can take now that, once successfully implemented, will act as a solid foundation for future activities. Well-thought out, consistent effort over time will lead to improved patient experience.

The following are identified priorities from the Lymphoma Coalition's perspective.

Lymphoma Coalition firmly believes that if we, patient organisations, and other key stakeholders work together, we can jointly bring about positive change.

RESEARCH PRIORITIES

1) There is still no cure for CLL.

The introduction of chemoimmunotherapy agents and targeted therapies have improved the outcomes of first-line treatment, but most patients with CLL relapse and require subsequent treatment. Of the clinical trials identified as involving CLL (globally), only 23% were first-line therapy trials. The optimisation of first-line treatment for CLL should remain a top priority given the potential to confer a greater benefit for a greater number of patients.

2) Clinical trials must be accessible for older patients.

Trials studying new treatment options or optimal therapy choices for patient with CLL must match the population of those diagnosed. This means the inclusion of older adults in trials, alongside tools to assess their function and frailty. Trial inclusion and exclusion criteria must also be carefully considered to ensure it does not unintentionally exclude the preferred patient population.

3) Therapy sequencing.

The introduction of novel, targeted therapies has changed the treatment landscape for CLL and improved care for some hard-to-treat prognostic subgroups. However, new challenges emerge when patients relapse on novel agents, and optimal sequencing strategies have not been established. Therapy sequencing strategies must be defined.

4) Reduced toxicity profiles.

Even new treatments can have an extensive side effect profile that can impact patients' quality of life. There is a continued need for better treatment options with fewer toxicities.

5) Minimal residual disease (MRD) assessment.

The role of MRD assessment in routine clinical practice for CLL needs to be better defined.

6) Treatment for Richter's Transformation.

Improved treatment options are needed for patients whose CLL undergoes Richter's Transformation (RT), especially for patients whose transformed CLL presents as DLBCL (90% of all RT cases). Generally, the DLBCL variant of RT has a poor prognosis because the disease responds poorly to the available DLBCL treatment regimens.

How LC can help:

While LC does not conduct or fund research related to medical care, we can do the following:

- Provide input to the early-stage development and subsequent review of clinical trials to ensure the inclusion of patient-relevant priorities and removal of participation barriers.
- LC will partner with all relevant stakeholders to promote a regulatory change focused on reducing bureaucracy associated with clinical trials. This will encourage more doctors and patients to participate and will facilitate low- and middle-income countries to join clinical research.
- LC is committed to finding ways to bring the clinical trial to the patient in need, on a country-by-country basis.
- Through the Lymphoma and CLL Community Advisory Board, LC helps build research that answers questions and examines outcomes that are important to patients, their caregivers, and clinicians. LC can help to validate and integrate reliable Quality of Life and Patient Reported Outcomes (PRO) measurements to systematically capture meaningful health outcomes.

EQUITABLE TREATMENT PRIORITIES

1) Access to novel therapies.

Certain subgroups of patients with CLL (e.g., del(17p) and/or *TP53* mutation, unmutated IGHV) respond poorly to chemoimmunotherapy. Yet targeted therapies were less accessible across all regions, with the exception of ibrutinib monotherapy. Access to targeted therapy regimens must be improved globally.

How LC can help:

- Continue to provide training to member patient organisations to increase their understanding of drug approval processes as well as advocacy techniques they can use to incite change locally, including the creation of an advocacy toolkit and member workshops. This will include how to effectively use both qualitative and quantitative data for an evidence-based approach to advocacy.
- Where extra support is needed, LC will provide individual mentoring to member groups to enable them to build and action their advocacy plans.
- Analyse data from the biennial *Global Patient Survey on Lymphomas & CLL* by disease status and geography so it can be used to support advocacy initiatives by members as well as inform the broader community.

2) Access to testing.

Numerous prognostic markers have been established for CLL. These can influence choice of treatment especially since therapy access is often limited to those with poor prognoses. Tests for mutations, markers, and chromosomal abnormalities are not readily accessible in all countries. This needs to change to ensure patients receive the best treatment. Additionally, increased patient education is needed around genetic markers and chromosomal abnormalities and how this impacts optimal treatment.

How LC can help:

- LC wrote a report on Genetic Markers in 2019. From this report, LC will create a quick reference sheet of biomarker tests used in CLL and their purpose.
- Include information on the importance of testing before every line of therapy for patients with CLL into an awareness campaign.
- Work alongside healthcare professional organisations to define minimum standards for testing and identify solutions for low-resourced communities.
- Use the above-mentioned advocacy initiative to help member organisations incite local change.

3) Pandemic response.

A consensus guideline for the management of patients with CLL during the Covid-19 pandemic and future infectious disease pandemics must be established. This must include clear indications for patients with and without a Covid-19 diagnosis. Additionally, it is crucial that patients with CLL be eligible to receive Covid-19 vaccinations, despite any doubts regarding immune response to vaccinations in this population, as well as priority access to any developed antivirals and treatments.

How LC can help:

- Track clinical practice guidelines related to Covid-19 from professional organisations and seek clarity on inconsistencies.
- Continue to create and compile Covid-19 resources for member patient groups to help them understand and manoeuvre through the latest research and recommendations.
- Advocate for access to vaccines, antivirals, and effective treatments in a timely manner for patients with lymphomas, including CLL.

IMPROVING PATIENT WELLBEING

1) Burden of fatigue.

Among patients with CLL/SLL who responded to the LC 2020 GPS, fatigue was the top reported symptom and treatment side effect affecting well-being, often for many years. Cancer-related fatigue and the repercussions it may have for patients before, during, and post treatment is an important factor that must be addressed.

How LC can help:

- LC champions the recognition of fatigue as a diminishing quality of life feature and will help to introduce active monitoring of fatigue in the lymphoma care pathway. This includes advocating for HCPs to follow the fatigue clinical practice guidelines established by NCCN and ESMO for each patient.
- Raise awareness of the impact of fatigue in an ongoing awareness campaign.
- Continue to recommend member patient organisations have information on fatigue available for patients, including resources to help patient's cope. LC published a toolkit related to fatigue in 2020.

2) Psychosocial impact.

A. **Patients in active surveillance.** The LC 2020 GPS showed that compared to the rest of the CLL/SLL population, a greater proportion of patients in active surveillance reported experiencing fear of disease progression, anxiety, and depression. Patients in active surveillance require more support for these specific issues, as well as ongoing reassurance that their symptoms are being actively monitored and that treatment will begin when necessary.

B. **Need for ongoing support.** The chronic nature of CLL means that many patients (not just those in active surveillance) will live with this disease for many years, and all patients require more support to manage the coupled long-term psychosocial issues that impact well-being.

C. **Communication with doctors.** It was clear in the LC 2020 GPS that a communication gap still exists surrounding psychosocial concerns; the two-way exchange of information between patients and their doctors continues to be impaired. Healthcare providers cannot be expected to provide all the information and support patients need, especially in light of time limitations; however, patients must be directed to the appropriate resources (e.g., patient organisations, other hospital or community-based resources).

How LC can help:

- Encourage the use of the terminology active surveillance or active monitoring instead of watch-and-wait, to help communicate to patients at this stage that their healthcare team is diligently observing and reacting to their health status to determine when is the optimal time for them to progress to the next phase of treatment. This is a defined, clinically validated stage of the treatment pathway.
- Use the GPS data to highlight the specific needs of patients to both medical and patient advocacy communities, highlighting the importance of patients being connected as early as possible to both credible information and emotional support.
- Continue to recommend member patient organisations have credible information on fear of cancer recurrence (FCR) available for patients, including resources to help patients cope. LC published a toolkit related to FCR in 2020.
- Build an evidence-based framework of systematic questions to guide physician-patient communication that will facilitate a useful dialogue with patients about their emotional health, physical concerns and their individual treatment plan and personal care pathway, ensuring discussions with patients are conducted in a patient-centric manner.
- Connect doctors and clinics with local patient organisations who can provide additional information and support to patients, often without the time limitations experienced in clinic.

Appendices

APPENDIX 1: CLINICAL DIAGNOSTIC TESTING GUIDELINES FOR CLL

Table 1: NCCN and ESMO diagnostic testing guidelines

Recommended Test	NCCN	ESMO
Immunohistochemistry (IHC)	X	X
Flow cytometry: presence and clonality of monoclonal B lymphocytes	X	X
Flow cytometry: immunophenotyping for cell surface markers CD19, CD20, CD5, CD23, CD10	X	X
Fluorescence in situ hybridization (FISH): detection of trisomy 12, del(11q), del(13q), del(17p), *TP53* sequencing	X	X
Molecular analysis: IGHV mutational status	X	X
Testing for Serum β2-microglobulin (B2M)		X

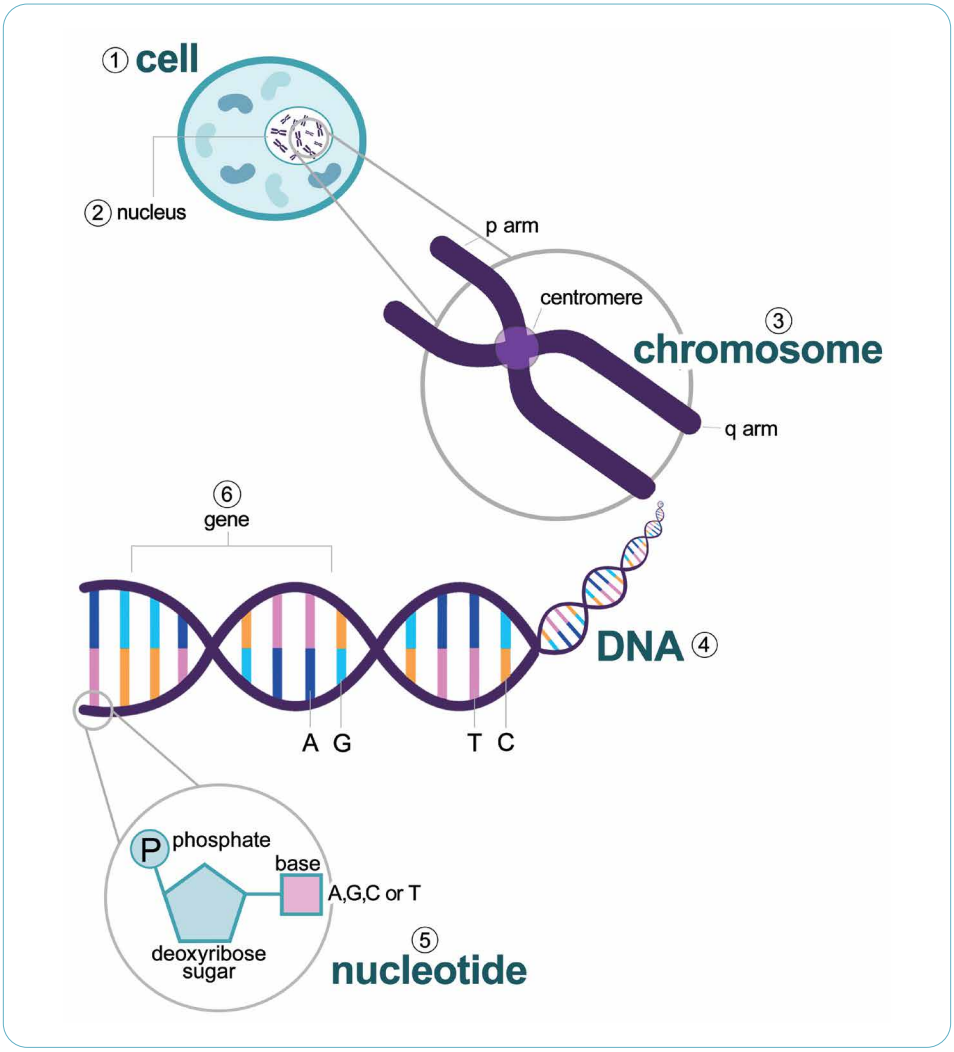
*In both guidelines, if diagnosis cannot be established through flow cytometry, bone marrow or fine needle aspirate is recommended

Table 2: iwCLL diagnostic and pre-treatment testing guidelines

Diagnostic Test	General Practice
Tests to Establish the Diagnosis	
CBC and differential count	Always
Immunophenotyping of peripheral blood lymphocytes	Always
Assessment Before Treatment	
History and physical, performance status	Always
CBC and differential count	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always
Chest radiograph	Always
Infectious disease status	Always
Additional Tests Before Treatment	
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	Not generally indicated
TP53 mutation	Always
IGHV mutational status	Always
Serum β2-microglobulin	Desirable
CT scan of chest, abdomen, and pelvis	Not generally indicated
MRI, PET scans	Not generally indicated
Abdominal ultrasound	Possible

APPENDIX II: CELL BIOLOGY BASICS RELATING TO GENETIC MARKERS, GENE MUTATIONS, AND CHROMOSOMAL ABNORMALITIES

Human bodies are made up of trillions of cells, and most cells contain a complete set of genes. Each person has thousands of genes that act like a set of instructions, controlling growth and how bodies work. Genes are made of DNA and are carried on thread-like structures called chromosomes. Chromosomes are stored in the nucleus of a cell; usually, a person has 46 chromosomes in each cell, 23 inherited from their mother and 23 from their father. These structures are described in further detail below.



1. **Cells**
   Cells are the basic unit of life. The human body is made up of trillions of cells which provide structure for the body, convert nutrients from food into energy, and carry out specialised functions. Cells contain the body's hereditary material.

2. **Nucleus**
   The nucleus is the cell's command and information processing centre. It has 2 major functions: it coordinates the cell's activities (growth, maturation, division); and it stores the cell's hereditary material which is called DNA.

3. **Chromosome**
   A chromosome is a thread-like structure made up of DNA that is tightly coiled around proteins called histones. This is how DNA is packaged for storage in the cell nucleus. Each chromosome contains many genes and is divided into 2 'arms' by a constriction point called the centromere. The short arm is called the 'p arm' and the long arm is called the 'q arm'. The centromere can be located in different places on different chromosomes, this is what gives a chromosome its shape, and it can be used to describe the location of specific genes.

4. **DNA**
   DNA, or deoxyribonucleic acid, is the hereditary material in humans. It is a double helix structure that resembles a twisted ladder. The information in DNA is stored as a code made up of 4 chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). The specific order of these bases determines the information available for building and maintaining an organism, much like how letters of the alphabet appear in different orders to form words and sentences. Each base is also attached to a sugar molecule and a phosphate molecule, and all 3 of these items together (base+ sugar+ phosphate) are called a nucleotide.

5. **Nucleotides**
   Nucleotides are arranged in 2 long parallel strands that bind together to form the DNA double helix structure. These strands bind together through base pairing; A binds with T, and C binds with G to form the steps of the ladder, and the sugar and phosphate molecules form the vertical side pieces of the ladder.

6. **Gene**
   A gene is the basic unit of heredity. Genes are made up of a segment DNA, and they can range in size from a few hundred DNA bases (A, C, G, T) to more than 2 million bases. Some genes act as instructions to make molecules called proteins. Genes are assigned a name and symbol; the symbol is a short combination of letters (and sometimes numbers) that represent an abbreviated version of the name.

What is a Gene Mutation?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. A gene mutation can range in size, affecting anywhere from a single DNA base pair (A&T, G&C) to a large DNA segment that involves multiple genes. Mutations can be hereditary (passed on from a parent) or acquired, meaning a change happens during a person's life that usually only affects certain cells. A person's health can be affected because mutations may lead to alterations in a protein's structure, changing the way the protein works, and affect the amount of proteins. Some mutations can change a cell from healthy to cancerous.

What is a Genetic Marker?

A genetic marker is a specific DNA sequence with a known physical location on a chromosome. It is described as an observable variation, which may arise because of a mutation or an alteration in the gene's location. Each chromosome has many genetic markers. While specific sequences may vary between individuals, there is enough consistency in the genetic code at that particular site on the genome to allow comparison between individuals. A marker can have functional consequences, for example, the function or expression of a gene can contribute directly to the development of a disease. A marker can also have no functional consequences but could be located very close to a functional variant (which does alter the function of a gene), which causes both the marker and the variant to be inherited together in the population at large.

Information taken from Lymphoma Coalition Genetic Markers report: lymphomacoalition.org/genetic-markers-in-lymphoma

APPENDIX III: TESTING FOR CLL BIOLOGICAL AND GENETIC MARKERS SUGGESTED IN CLINICAL PRACTICE GUIDELINES

Table 1. Biologic and genetic markers to test for in CLL as recommended by the NCCN, ESMO, and iwCLL

Abnormality	Test	NCCN 2020	ESMO 2020	iwCLL 2019	Marker Type*
Chromosomal Abnormality					
t(11;14)	FISH	x	x	x	D
t(11q;v)	FISH	x			D
11q del	FISH	x	x	x	P
13q del	FISH	x		x	P
17p del	FISH	x	x	x	P
Trisomy 12	FISH	x	x	x	P
Complex karyotype	Chromosome-banding analysis	x			P
Gene Mutation					
TP53	FISH	x	x	x	P
IGHV (mutational status)	Molecular analysis	x	x	x	P
Protein/Antigen Expression					
Cyclin D1	Immunohistochemistry	x	x		D
ZAP-70	Flow cytometry	x			P
CD38	Flow cytometry	x			P
CD49d	Flow cytometry	x			P

*D= Diagnostic; P= Prognostic

APPENDIX IV: THERAPY ACCESS BY-COUNTRY FOR CLL

Table 1. CLL therapy access by-country for Lymphoma Coalition member countries

	Chemoimmunotherapy			Targeted Therapies						
Europe	**FCR***	**Bendamustine + Rituximab**	**Obinutuzumab + Chlorambucil**	**Ibrutinib Monotherapy**	**Ibrutinib + Rituximab**	**Acalabrutinib Monotherapy**	**Idelalisib + Rituximab**	**Venetoclax Monotherapy**	**Venetoclax + Rituximab**	**Venetoclax + Obinutuzumab**
Belgium										
Bulgaria										
Croatia										
Czech Republic										
Denmark										
Finland										
France										
Germany										
Greece										
Hungary										
Ireland										
Italy										
Latvia										
Lithuania										
Macedonia										
Netherlands										
Norway										
Poland										
Portugal										
Romania										
Russian Federation										
Serbia										
Slovakia										
Slovenia										
Spain										
Sweden										
Switzerland										
Turkey										
Ukraine										
United Kingdom										

Data as of January 2021
FCR: fludarabine, cyclophosphamide, rituximab
Notes: Accessible defined as therapy being available to patient through public healthcare

Key
- Accessible defined as therapy being available to patient through public healthcare
- Therapy funded through a special access program within that country
- Therapy not funded
- No information found whether therapy is available for this subtype

Table 1. CLL therapy access by-country for Lymphoma Coalition member countries, continued

	Chemoimmunotherapy			Targeted Therapies						
North America	FCR*	Bendamustine + Rituximab	Obinutuzumab + Chlorambucil	Ibrutinib Monotherapy	Ibrutinib + Rituximab	Acalabrutinib Monotherapy	Idelalisib + Rituximab	Venetoclax Monotherapy	Venetoclax + Rituximab	Venetoclax + Obinutuzumab
United States										
Canada										
South America	FCR*	Bendamustine + Rituximab	Obinutuzumab + Chlorambucil	Ibrutinib Monotherapy	Ibrutinib + Rituximab	Acalabrutinib Monotherapy	Idelalisib + Rituximab	Venetoclax Monotherapy	Venetoclax + Rituximab	Venetoclax + Obinutuzumab
Argentina										
Barbados										
Brazil										
Colombia										
Uruguay										
Venezuela										
Mexico										
Asia Pacific	FCR*	Bendamustine + Rituximab	Obinutuzumab + Chlorambucil	Ibrutinib Monotherapy	Ibrutinib + Rituximab	Acalabrutinib Monotherapy	Idelalisib + Rituximab	Venetoclax Monotherapy	Venetoclax + Rituximab	Venetoclax + Obinutuzumab
China										
Hong Kong										
India										
Japan										
Republic of Korea										
Singapore										
Australia										
New Zealand										
Middle East & Africa	FCR*	Bendamustine + Rituximab	Obinutuzumab + Chlorambucil	Ibrutinib Monotherapy	Ibrutinib + Rituximab	Acalabrutinib Monotherapy	Idelalisib + Rituximab	Venetoclax Monotherapy	Venetoclax + Rituximab	Venetoclax + Obinutuzumab
Israel										
Algeria										
Morocco										
South Africa										

Data as of January 2021
FCR: fludarabine, cyclophosphamide, rituximab
Notes: Accessible defined as therapy being available to patient through public healthcare

Key
- Accessible defined as therapy being available to patient through public healthcare
- Therapy funded through a special access program within that country
- Therapy not funded
- No information found whether therapy is available for this subtype

APPENDIX V: PHASE II AND PHASE III CLINICAL TRIALS FOR CLL

Table 1. Number of Phase II and Phase III clinical trials for 15 lymphoma subtypes

Total number of Phase II and III trials globally = 907

Subtype	Phase II	Phase III	Total	% All Trials*	Subtype Specific Trial	% of Subtype Total	First Line Trials	Relapse Trials	Targeted Therapy Trials	% of Targeted Therapy Trials	Chemo-immuno-therapy (CI) Trials	% of CI Therapy Trials
Adult T-cell leukemia	48	0	48	5%	4	8%	4	38	30	63%	8	17%
Anaplastic large cell	87	1	88	10%	10	11%	12	66	55	63%	17	19%
Burkitt's	73	4	77	8%	2	3%	8	62	48	62%	16	21%
Chronic Lymphocytic Leukaemia	211	30	241	27%	133	55%	56	158	202	84%	24	10%
Cutaneous T-cell	77	4	81	9%	20	25%	4	61	45	56%	13	16%
Diffuse large B-cell	305	33	338	37%	139	41%	64	254	228	67%	84	25%
Extranodal natural killer T-cell	79	7	86	9%	33	38%	16	55	54	63%	9	10%
Follicular	242	33	275	30%	58	21%	44	212	193	70%	56	20%
Hairy cell leukaemia	44	0	44	5%	7	16%	2	36	30	68%	7	16%
Hodgkin	113	10	123	14%	89	72%	37	82	71	58%	35	28%
Mantle cell	210	15	225	25%	63	28%	36	174	164	73%	40	18%
Marginal zone	132	12	144	16%	12	8%	17	113	105	73%	23	16%
Peripheral T-cell	117	2	119	13%	26	22%	17	92	64	54%	26	22%
Primary cutaneous anaplastic large cell	38	0	38	4%	0	0%	1	32	27	71%	4	11%
Waldenstrom macroglobulinaemia	85	9	94	10%	13	14%	12	69	73	78%	10	11%

Data as of January 2021

*% All trials is calculated as the total number of trials for the subtype divided by 907, which is the total number of Phase II and III trials identified for all subtypes included in this analysis (there is overlap between subtypes represented in a trial)

Targeted therapy trials + chemoimmunotherapy trials will not equal the total number of trials for the subtype (standard chemotherapy and biosimilars are excluded)

Table 2. Number of Phase II and Phase III CLL clinical trials by LC member country

LC Member Country	Total P2 and P3 CLL Trials	Targeted Therapy P2 and P3 CLL Trials	Chemoimmuno-therapy P2 and P3 CLL Trials
All CLL Trials	241	202	24
Europe			
Belgium	13	12	1
Bulgaria	3	3	0
Czech Republic	8	7	1
Denmark	14	12	2
France	19	18	1
Finland	5	4	1
Germany	29	24	4
Greece	2	2	0
Hungary	7	6	1
Ireland	5	4	1
Italy	23	21	2
Latvia	0	0	0
Lithuania	0	0	0
Netherlands	17	15	2
Norway	3	2	1
Poland	19	17	2
Portugal	3	2	1
Romania	2	1	1
Slovakia	1	1	0
Slovenia	0	0	0
Spain	18	17	1
Sweden	14	11	3
United Kingdom	26	23	2
Croatia	1	1	0
Macedonia	0	0	0
Russian Federation	10	9	1
Serbia	0	0	0
Switzerland	5	5	0
Turkey	6	6	0
Ukraine	2	2	0

LC Member Country	Total P2 and P3 CLL Trials	Targeted Therapy P2 and P3 CLL Trials	Chemoimmuno-therapy P2 and P3 CLL Trials
All CLL Trials	241	202	24
Asia Pacific			
China	34	33	1
India	0	0	0
Japan	2	2	0
Republic of Korea	7	6	1
Singapore	0	0	0
Australia	20	19	1
New Zealand	11	10	1
Latin America			
Argentina	4	4	0
Brazil	5	5	0
Colombia	1	1	0
Uruguay	0	0	0
Venezuela	0	0	0
Mexico	4	4	0
North America			
Barbados	0	0	0
Canada	12	10	2
United States	169	137	19
Middle East & Africa			
Iraq	0	0	0
Israel	10	9	1
Algeria	0	0	0
Morocco	0	0	0
South Africa	1	1	0

Data as of January 2021

Methodology

Trial sources - Clinicaltrials.gov, the European Union Clinical Trials Register, the Australian Cancer Trials, and the World Health Organization website

Only Phase II and III active, interventional (therapy-based) trials were considered

Targeted therapies for CLL - Targeted therapies have been approved since rituximab or still in clinical development

Availability of novel as well as standard therapies was determined through the LC Global Database, which is kept current through a quarterly review of member country regulatory and reimbursement websites, medical journals and general media press releases

Glossary

Age-standardised incidence rate (ASIR)
The average number of new cases of cancer per 100,000 people in an age group. Standardisation is required when comparing several populations of different ages because age has a powerful influence on the risk of acquiring and/or dying from cancer.

Alkylating agents
Alkylating agents are chemotherapy drugs that work by keeping the cancer cell from reproducing (making copies of itself) by damaging its DNA (genetic material).

Allogeneic haematopoietic stem cell transplantation
A procedure where a patient receives healthy stem cells (blood-forming cells) to replace their own stem cells that have been destroyed. An allogeneic haematopoietic cell transplant uses a donor's stem cells. The donor is usually a relative of the patient, but unrelated donors or umbilical cord blood can be used in some cases.

Antigens
An antigen is something that triggers an immune response in the body, especially the production of antibodies. This can be either a toxin or foreign substance that the immune system recognises should not be present (e.g., bacteria, viruses) or protein originating from within the body.

Anti-CD20 antibody
CLL cancer cells come from B lymphocytes (white blood cells), which have a marker on their surface called CD20 (a protein). The anti-CD20 antibody is created to recognise CD20, which allows it to attach to the B lymphocyte in order to destroy it (i.e., killing the cancer cell as a result).

B cell lymphoma 2 (BCL-2) protein
This protein-type is a key regulator of the intracellular (within a cell) pathway that leads to apoptosis (programmed cell death). Altering the balance of BCL-2 proteins causes cells to not die when they are supposed to (evading apoptosis) and allows for the extended survival of cancer cells.

B cell receptor signalling
Both normal cells and cancer cells (e.g., CLL cells) have B cell receptors on their surface. B cell receptor functioning is needed for antibody production. Abnormal function of the B cell receptor (and the signals it produces) is associated with B cell cancers, including CLL. In CLL, the B cell receptor (once activated) provides signals for the survival and proliferation of CLL cells. The signal pathway that is initiated by B cell receptor activation is now the target of many new treatments.

B-symptoms
Unexplained fever, drenching night sweats, and loss of more than 10% of body weight over six months without any changes in diet or exercise.

Bruton's tyrosine kinase
A protein kinase that plays a crucial role in oncogenic (cancerous) signalling pathways. Abnormal activation (or mutation) of Bruton's tyrosine kinase drives changes in cell growth, survival, movement, and metabolism, as well as helps cancer cells to evade the anti-tumour response. Bruton's tyrosine kinase is critical for the survival of cancer cells in various B cell cancers (including CLL).

Chimeric antigen receptor therapies
A treatment that modifies a patient's or a donor's immune cells to express a receptor on their surface. The receptor recognises and binds to specific structures (antigens) on the surface of cancer cells, and once bound, can destroy the cancer cell. In CAR T-cell therapy, it is the patient's own T cells that are modified.

Chromosome
Part of a cell that contains genetic information. All human cells contain 46 chromosomes (except for sperm and eggs).

Clinical trials
Clinical trials are research studies used to determine if a new therapy, surgery or behavioral intervention is safe and effective in people.

Comorbidities
The condition of having two or more diseases at the same time (e.g., cancer and diabetes).

Complete blood count (CBC) with differential
A measure of the number of white blood cells, red blood cells, and platelets in the blood, including the different types of white blood cells (neutrophils, lymphocytes, monocytes, basophils, and eosinophils). A complete blood count also measures the amount of hemoglobin (substance in blood that carries oxygen) and hematocrit (the amount of whole blood that is made up of red blood cells). It is useful for diagnosing and monitoring many conditions.

Deauville score
A five-point scale used to stage and asses initial treatment response in certain lymphomas. The scale ranges from 1 to 5, where 1 is best (no uptake or no residual uptake) and 5 is worst (markedly increased uptake or any new lesion).

Flow cytometry
A laboratory test that measures the number of cells, the percentage of live cells, and certain cell characteristics (e.g., shape, size) in a sample of blood, bone marrow, or other tissue. This test also looks for the presence of tumour markers (e.g., antigens) on the surface of cells. Cells are stained with a dye that is light-sensitive, placed in a fluid, and then passed one at a time through a light beam. Measurements are taken based on how the cells react to the light beam.

Heterogeneity
Made up of elements or ingredients that are not alike.

Humoral response
A humoral response is when the body produces antibodies against a specific antigen (e.g. a virus).

Intubation
Inserting a tube into a patient's throat to help move air in and out of the lungs.

Lymphoid neoplasms
A neoplasm is an abnormal mass of tissues that forms when cells grow and divide more than they should, or do not die when they are supposed to. A neoplasm can be benign (non-cancerous) or malignant (cancerous). A lymphoid neoplasm arises from the malignant (cancerous) transformation of normal lymphoid cells at various stages of differentiation (cells changing from one type of cell to another). Lymphoid neoplasms include lymphoma, myeloma, and lymphoid leukaemia.

Median
The middle value in a set of measurements.

Memory B cells
Memory B cells are part of the adaptive immune system in the human body. Memory B cells provide protection against recurring infectious agents (they remember the virus or bacteria they fought previously). Memory B cells live in the body for a long time, even after all the viruses/bacteria from the first infection have been destroyed. They stay in ready-mode and are able to quickly recognise and attack any returning viruses or bacteria.

Monoclonal B-cell lymphocytosis (MBL)
A non-cancerous condition which causes an increased number of abnormal B cells called lymphocytes (white blood cells) in the blood. This condition is seen as a precursor (pre-cancerous) condition to CLL.

Naïve B cells
B cells, or B lymphocytes, develop and mature in the bone marrow. A naïve B cell is one that has matured and entered the bloodstream but has not yet transformed into a new type of cell that has a specific purpose. Naïve B cells travel through the lymphatic system until they either become memory B cells or encounter the appropriate antigen and start the activation process.

***NOTCH1* mutation**
A mutation that is expressed in the *NOTCH1* gene of some patients with CLL. Patients with CLL who express a mutation in the *NOTCH1* gene are associated with an unfavourable prognosis (e.g., shorter treatment-free survival, increased risk for Richter's Transformation). This gene mutation is detected in approximately 10% of CLL cases at presentation. Patients with unmutated IGHV are more likely to have the *NOTCH1* mutation.

Overall survival (OS)
The length of time from the date of diagnosis, or from the start of a treatment for a disease (e.g., cancer) that patients with the disease are still alive. Measuring overall survival in clinical trials is one way to see how well a new treatment works.

Passive immunity
Passive immunity means that a person is given antibodies to a disease rather than producing them through their own immune system.

PET scan
A positron emission tomography scan, or PET scan, is a procedure where a small amount of radioactive glucose (sugar) is injected into a vein, and then a scanner is used to make computerised pictures of areas inside the body where the glucose is absorbed. A PET scan can be used to find cancer cells in the body because they take up more glucose than normal cells.

Phase II clinical trial
The part of a research study where the therapy under review is administered to a larger group of patients (typically up to a few hundred) with the disease or condition for which the drug/therapy is being developed. Key focuses of Phase II clinical trials include initial assessment of effectiveness and further assessment of safety (of the drug/therapy), as well as determining the optimal dose or doses of a drug.

Phase III clinical trial
The part of a research study where the therapy under review is administered to many hundreds or thousands of participants from patient populations for which the drug/therapy is eventually intended to be used. Participants are assigned to receive either the drug/therapy being studied or are assigned to a control group where they will receive the current standard of care or a placebo. Phase III clinical trials are designed to determine whether or not the drug/therapy being studied offers a treatment benefit, to provide more detailed safety data, and to serve as the basis for product labelling.

Phosphatidylinositol 3-kinase (PI3K)
The phosphatidylinositol 3-kinase (enzyme) pathway regulates various cell processes such as cell growth, proliferation, differentiation (a cell transforming into a new type of cell), survival, and intracellular (within a cell) trafficking. Mutational events that lead to the over activation of this pathway result in cancers.

Prognostic (prognosis)
The likely outcome or course of a disease, including the chance of recovery or recurrence.

Progression-free survival (PFS)
The length of time during and after the treatment of a disease that a patient lives with the disease without it getting worse. Measuring progression-free survival in clinical trials is one way to see how well a new treatment works.

Purine analogues
When a new cell in the human body is formed, it goes through a series of phases to become a fully functioning (mature) cell. This process is called the cell cycle. Chemotherapy drugs target cancer cells at different phases of the cell cycle. Purine analogue chemotherapy agents work best in the S-phase of cell division when cells are growing and dividing quickly. They work by preventing the continued growth of DNA of the cancer cell (DNA synthesis), which prevents cell division. They do this by replacing the natural substances (purines) that normally act as the building blocks in DNA molecules. In other words, they mimic the nutrients that the cancer cell needs to grow, tricking the cell into consuming them so eventually it starves to death.

Signalling pathways
A group of molecules work together to control one or more cell functions, such as cell division or death. When the first molecule in a pathway receives a signal, it activates another molecule. This process continues until the last molecule is activated and the cell function occurs. If the activation in the signalling pathway is abnormal, it can result in cancer.

Spleen tyrosine kinase
Spleen tyrosine kinase is required for various processes of B-cell development. It is also recognised as a promoter of cell survival in numerous cancer cell types, so it has attracted major interest as a target for novel anti-cancer therapies.

Surrogate end-point
Can be used in clinical trials as an indicator in place of something else to determine if the treatment works. For example, endpoints of 'shrinking tumour' or 'lower biomarker levels' can be used instead of stronger indicators like 'longer survival'. These endpoints are often used so that the results of a clinical trial can be measured sooner.

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